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AGGIORNAMENTI IN EMATOLOGIA

FAENZA, Hotel Vittoria | 7 Giugno 2018 |

Responsabile Scientifico Francesco Lanza

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

- ✓Manifestazioni ematologiche in corso di malattie epatiche
- ✓Manifestazioni ematologiche maligne del fegato
- ✓Disordini vascolari del fegato
- ✓Sinusoidal obstructive syndrome (SOS)/Veno Occlusive disease (VOD)
- ✓GVDH
- ✓Riattivazione Virale in corso di Chemioterapia /MAb

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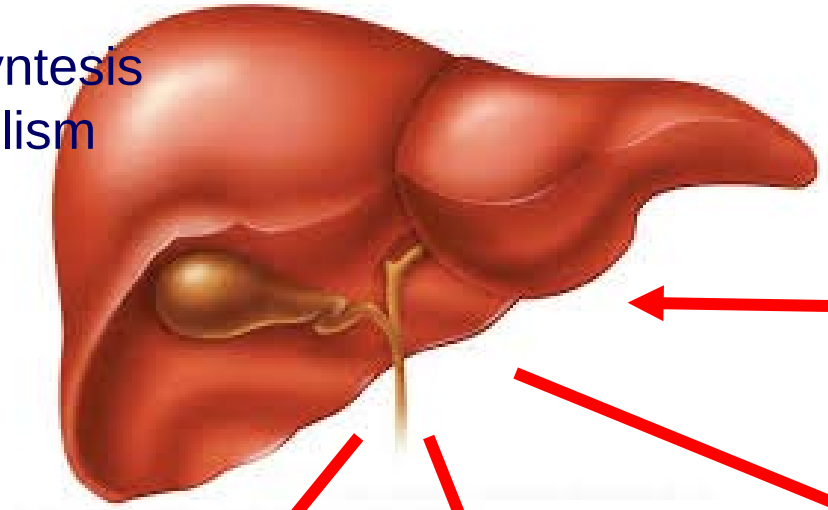
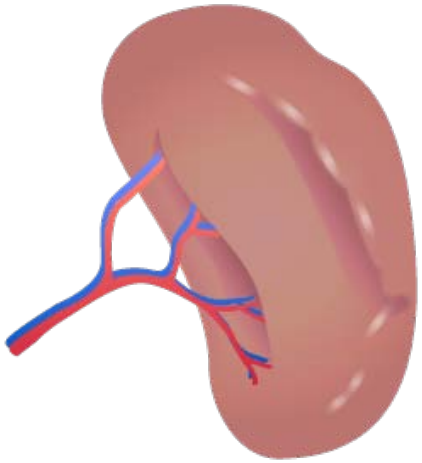
Schematic diagram illustrating select functions of the liver relevant to the hematologic manifestations of liver disease

- Protein biosyntesis
- Lipid metabolism
- Iron Storage



Portal blood flow



Hepcidin

Spleen
- Platelets
- Leukocytes
- Red Cells

Coagulation Factor
- Procoagulant
- Anticoagulant

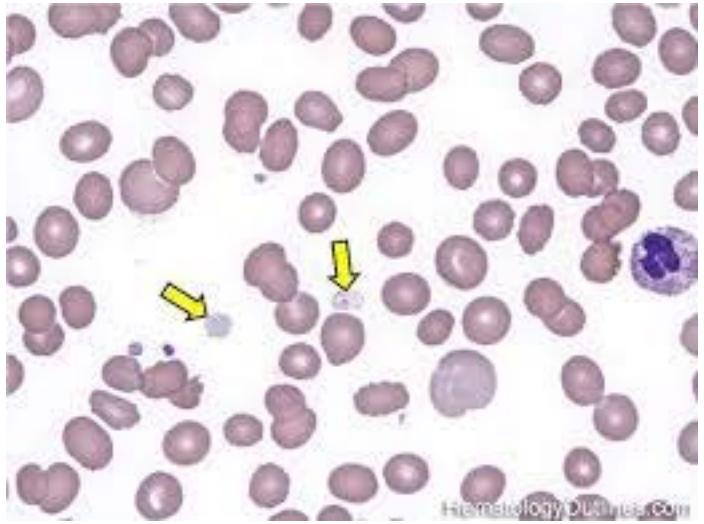
Hematopoietic Growth factor
- Thrombopoietin
- Erytropoietin (~10%)

Functions of the liver relevant to the hematologic manifestations

- Numbered clotting factors (II, V, VII, IX, X, XI) and the structural protein fibrinogen (factor I) are synthesized primarily in hepatocytes
- Aanticoagulant proteins such as protein C, protein S, and antithrombin
- Site for the constitutive production of erythropoietin (about 10%)
- Primary site for the synthesis of thrombopoietin
- Control of available iron through hepatic synthesis of hepcidin in response to infection, inflammation, or replete iron stores directly affects the erythropoietic response
- Primary site for iron storage, containing an amount of iron in the body second only to the erythron (generally about 1 g in an adult)
- A central synthetic and regulatory role in lipid metabolism, the liver is responsible for the requisite membrane composition of lipids and cholesterol needed for optimal red blood cell deformability.

Thrombocytopenia in chronic liver disease

- 76 % of cirrhotic patients
- 75.000/µL-150.000/µL(mild) minimal clinical significance
- 50.000/µL-75.000/µL (moderate) 13%
- <50.000/µL (moderate/severe) significant morbidity

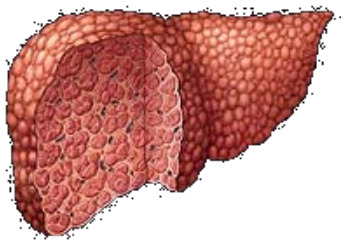


Pathophysiological Basis

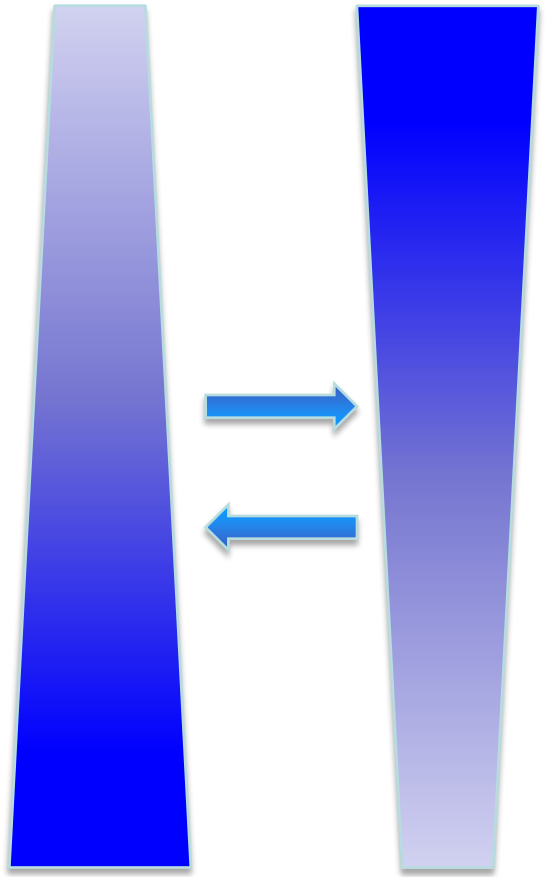
Healthy Liver

Chronic Hepatitis

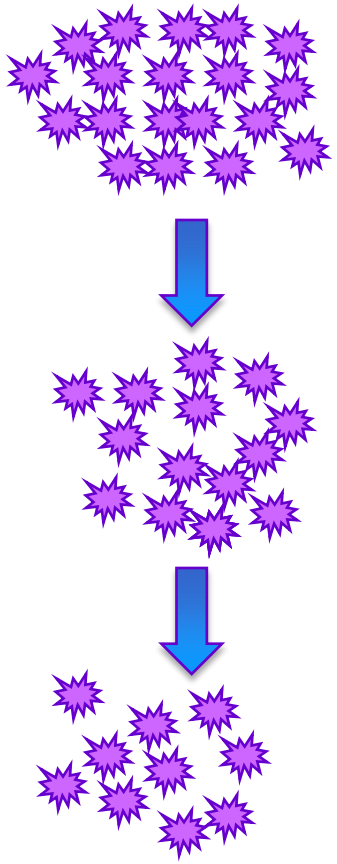
Liver Cirrhosis



Portal pressure **Liver Function**

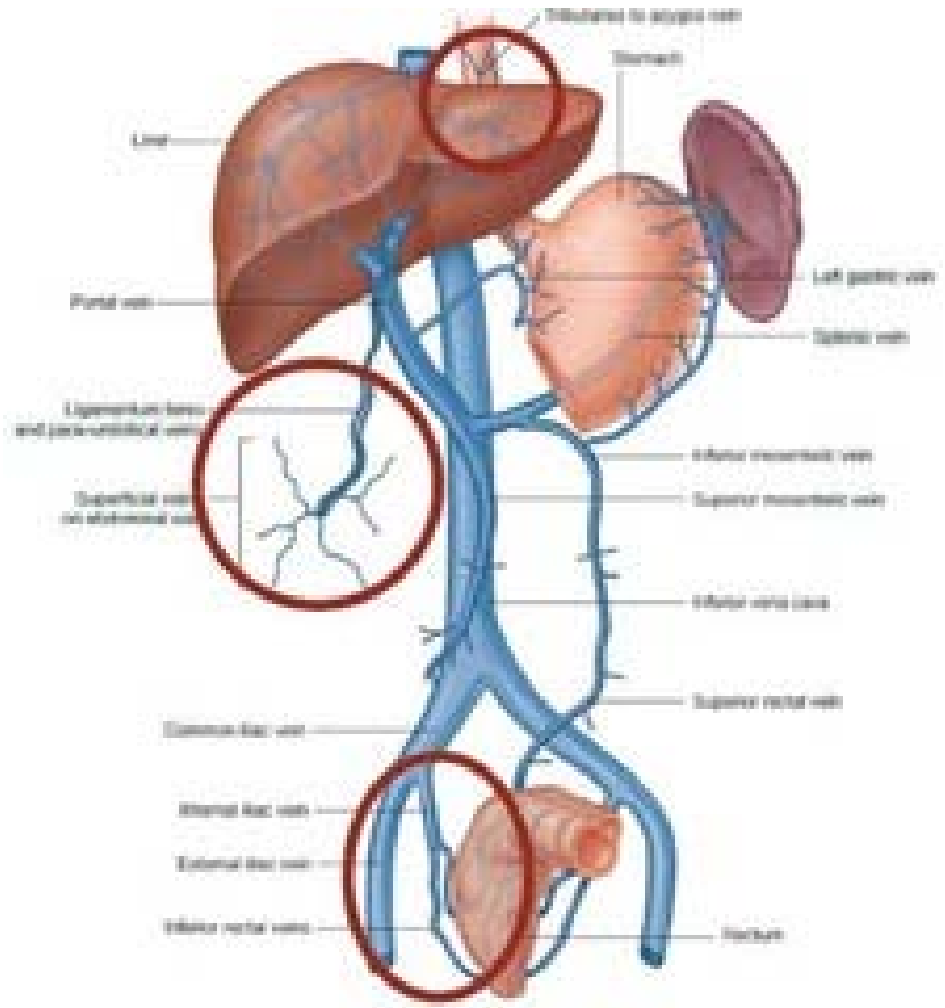


Platelets



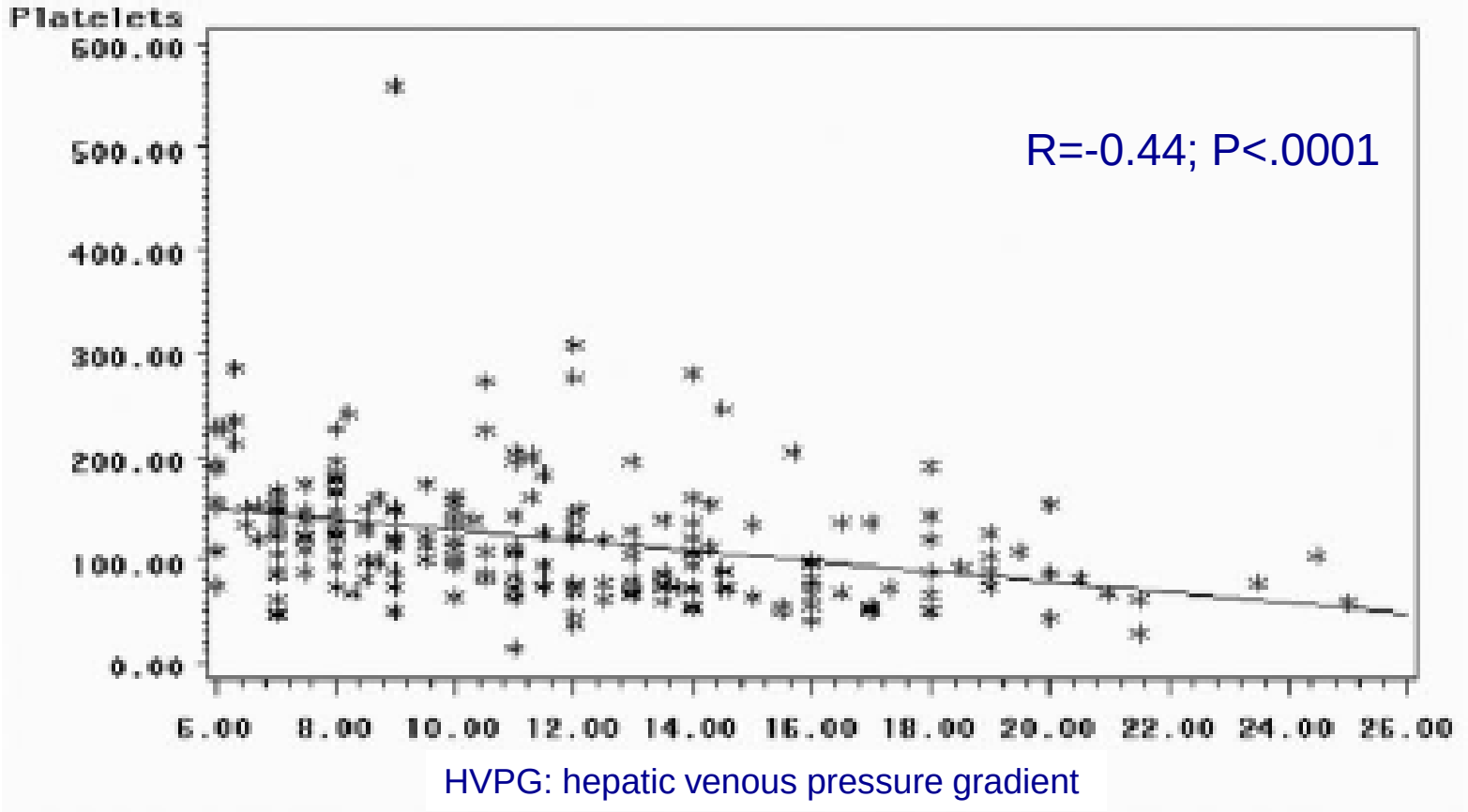
Giannini EG et al Curr Opin Hematol 2008

Platelet Count and portal pressure



Correlation between the platelet count and HVPG in cirrhosis

213 patients with compensate cirrhosis and PHT, without varices



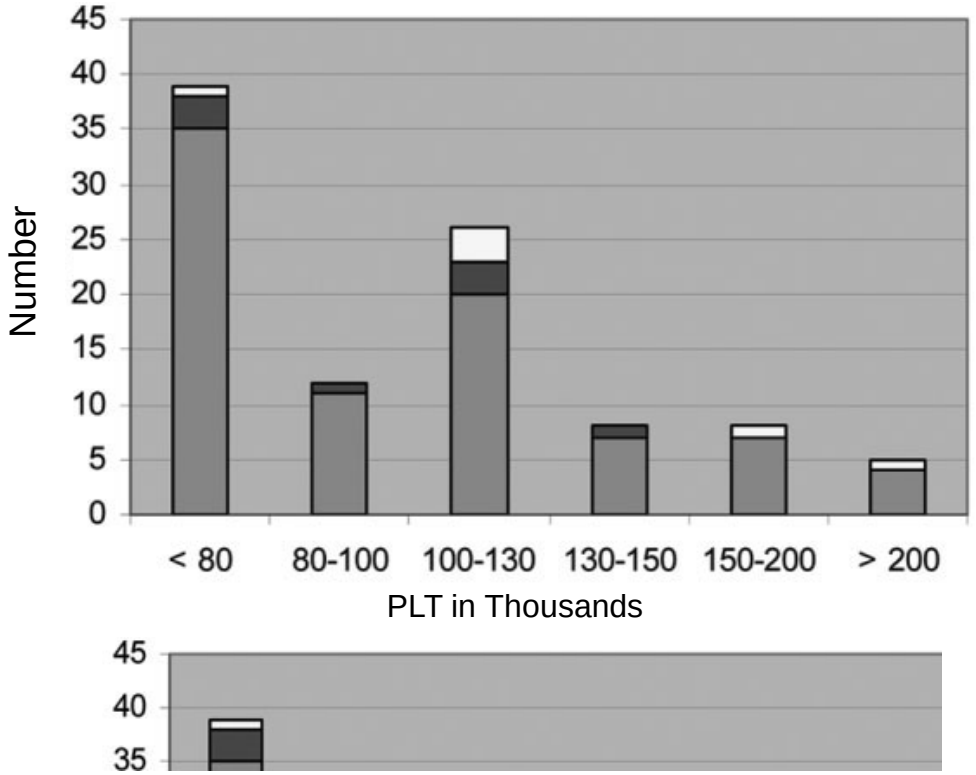
HVPG: hepatic venous pressure gradient

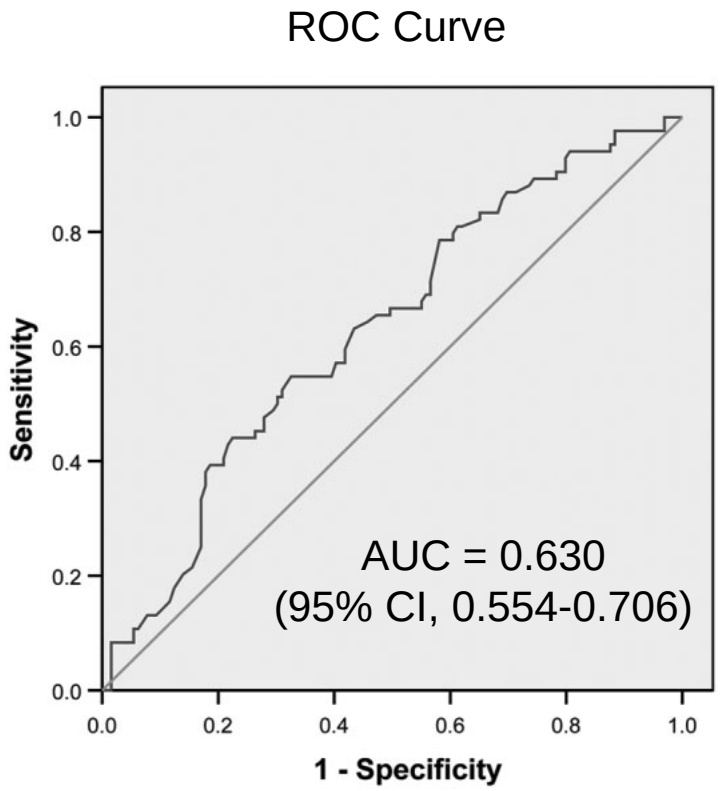
Median follow-up 54.9 months, 84 patients developed GEV; PLT >150,000 in 15%

Qamar AA e al Hepatol 2008

Platelet Count for the Noninvasive Diagnosis of Oesophagel Varices

Median platelet count at time of varices development =91,000/mm^3

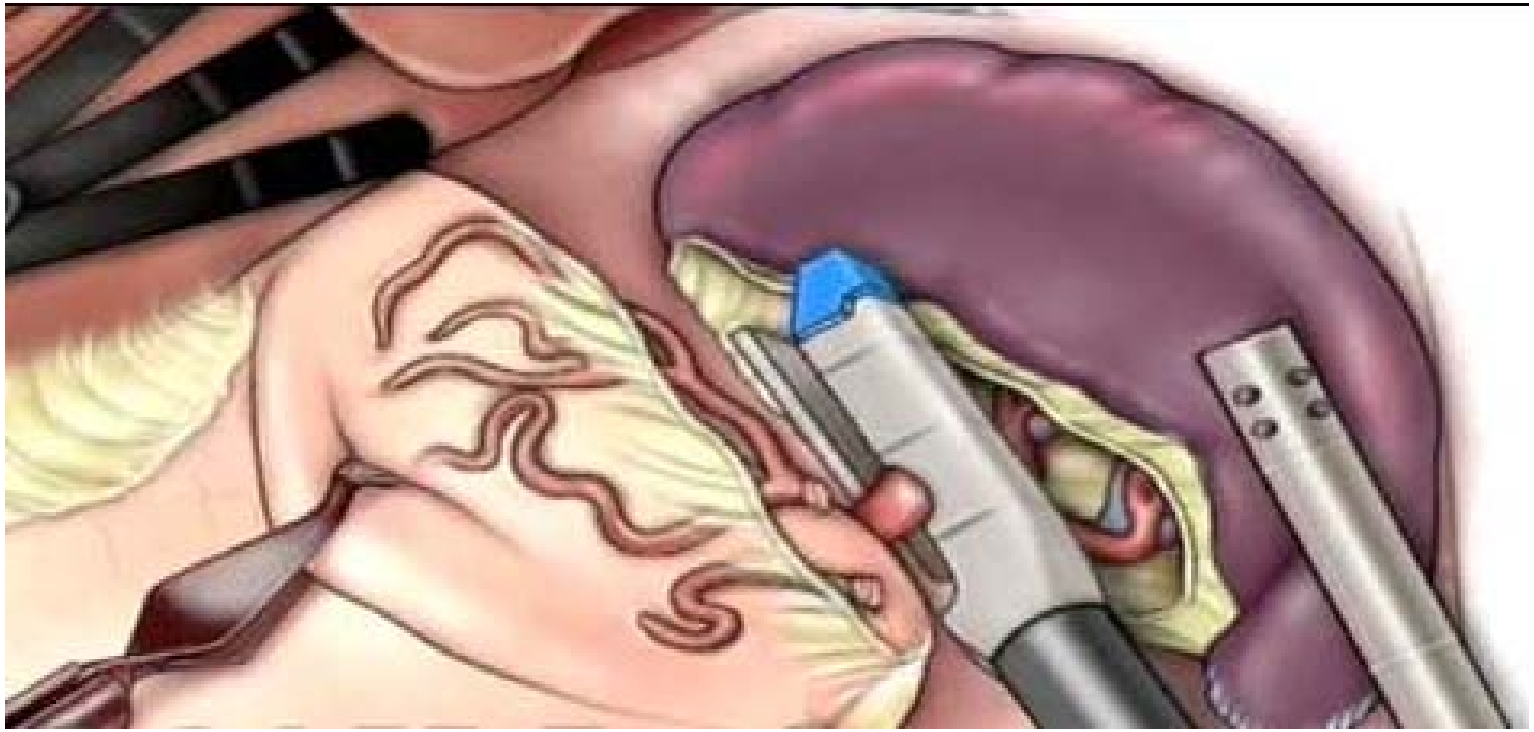




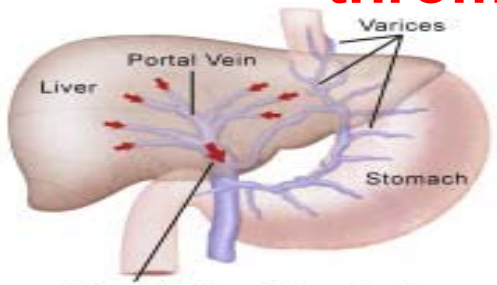
Small varices(SV) large varices (LV) variceal hemorrhage (VH)

Qamar AA et al Clin Gastroenterol Hepatol 2009

Treatment aimed at reversing portal hypertension do not always correct thrombocytopenia



Cause or contribute to the development of thrombocytopenia in chronic liver disease

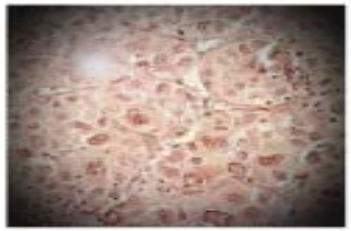


Portal Hypertension/
Hypersplenism

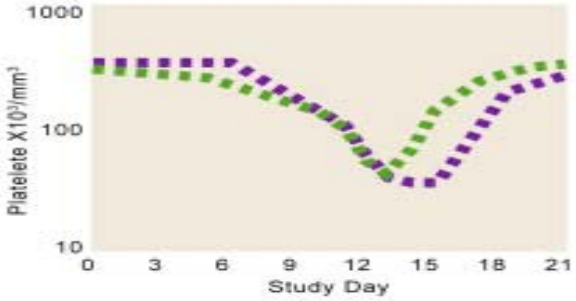
Cirrhosis

Anti-Platelet Antibodies

Thrombocytopenia



Hepatocellular Carcinoma/
Chemotherapy

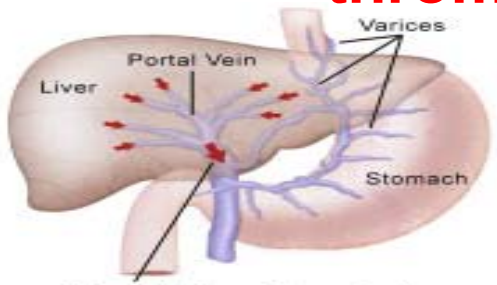


Viral Suppression/
Antiviral Therapy

Decreased Thrombopoietin
Levels/Activity

Afdha N J Hepatol, 2008

Cause or contribute to the development of thrombocytopenia in chronic liver disease



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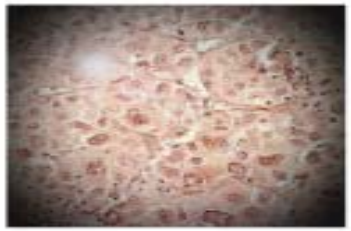

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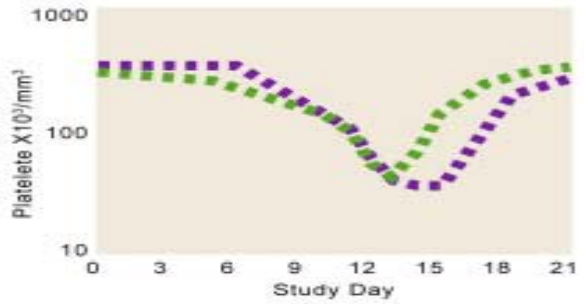
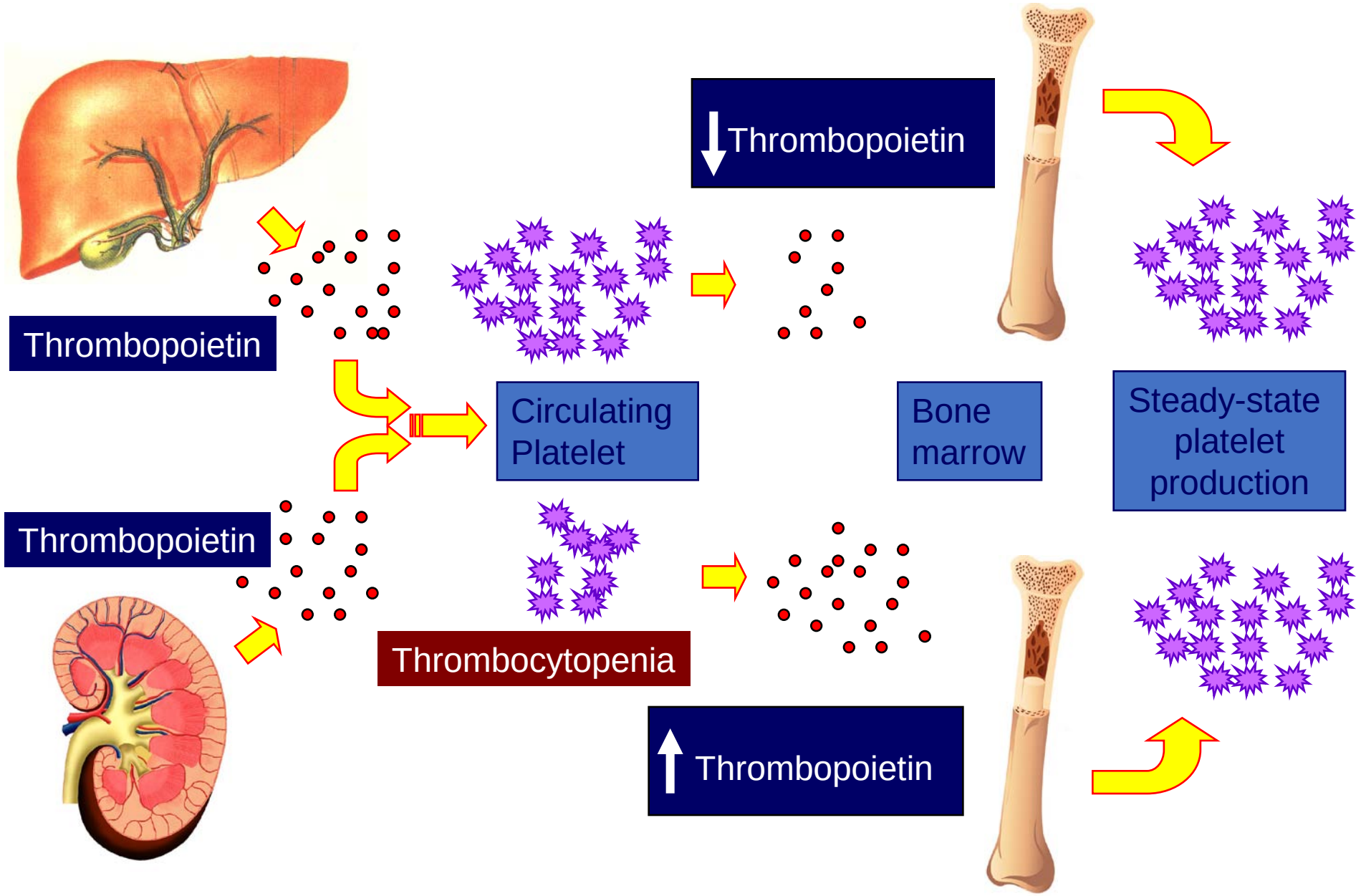


Viral Suppression/
Antiviral Therapy

Decreased Thrombopoietin
Levels/Activity

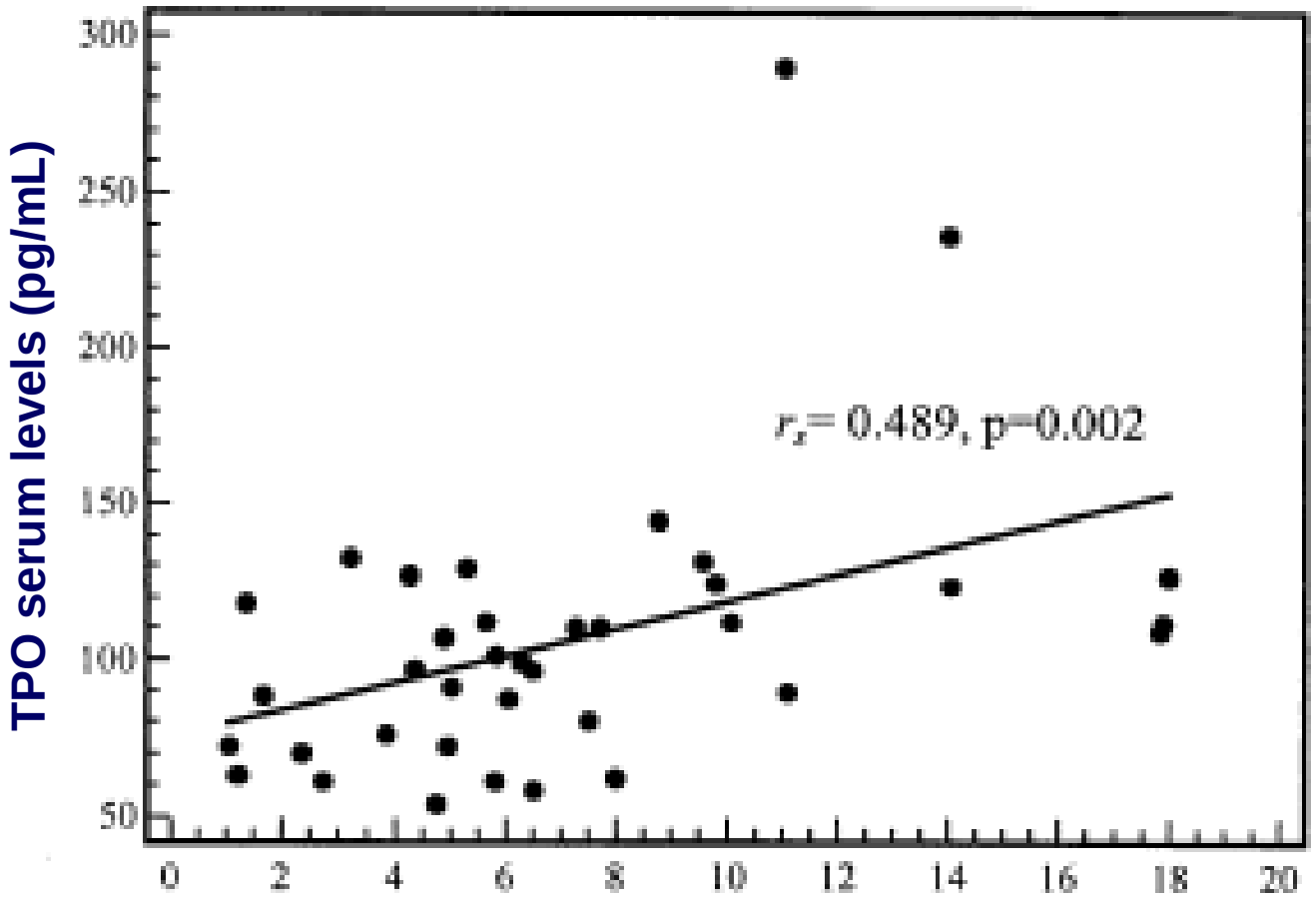
Afdha N J Hepatol, 2008

A Model of Thrombopoietin Regulation



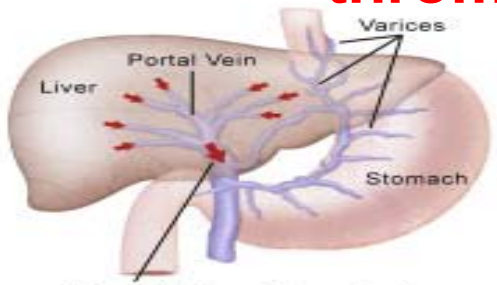
Kaushansky K N Eng J Med 1998

TPO Serum Levels Decrease as Liver Function Worsens



Giannini E et al Am J Gastroenterol 2003

Cause or contribute to the development of thrombocytopenia in chronic liver disease



Portal Hypertension/
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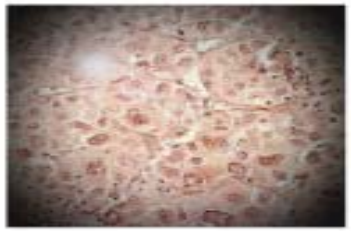
Cirrhosis

Anti-Platelet Antibodies

Thrombocytopenia



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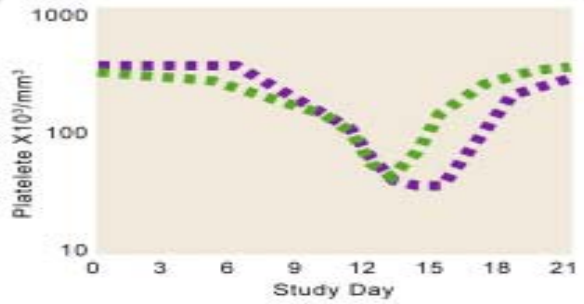

Viral Suppression/
Antiviral Therapy

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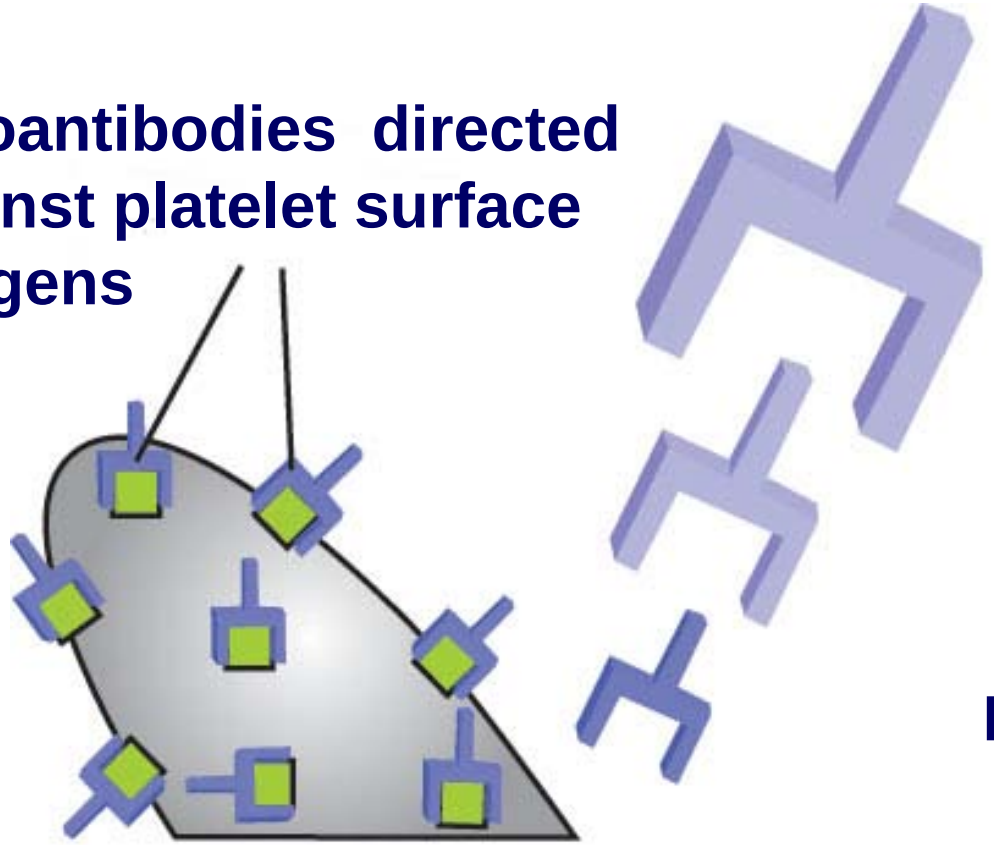
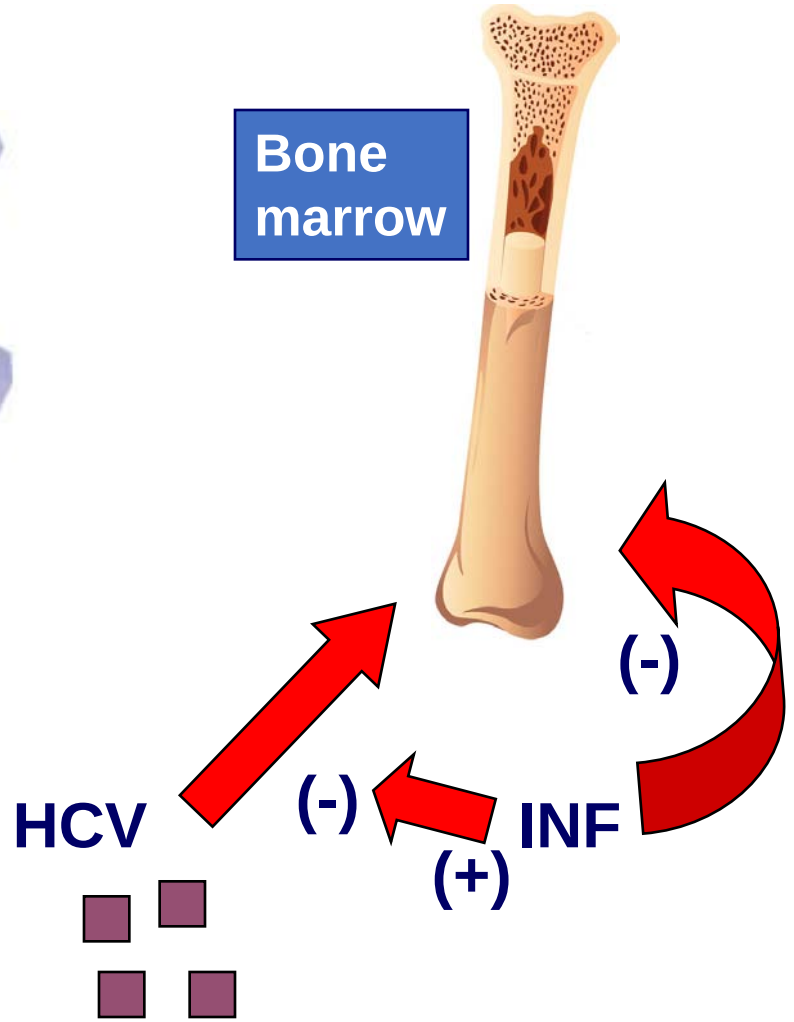
Afdha N J Hepatol, 2008

Autoimmune mechanism

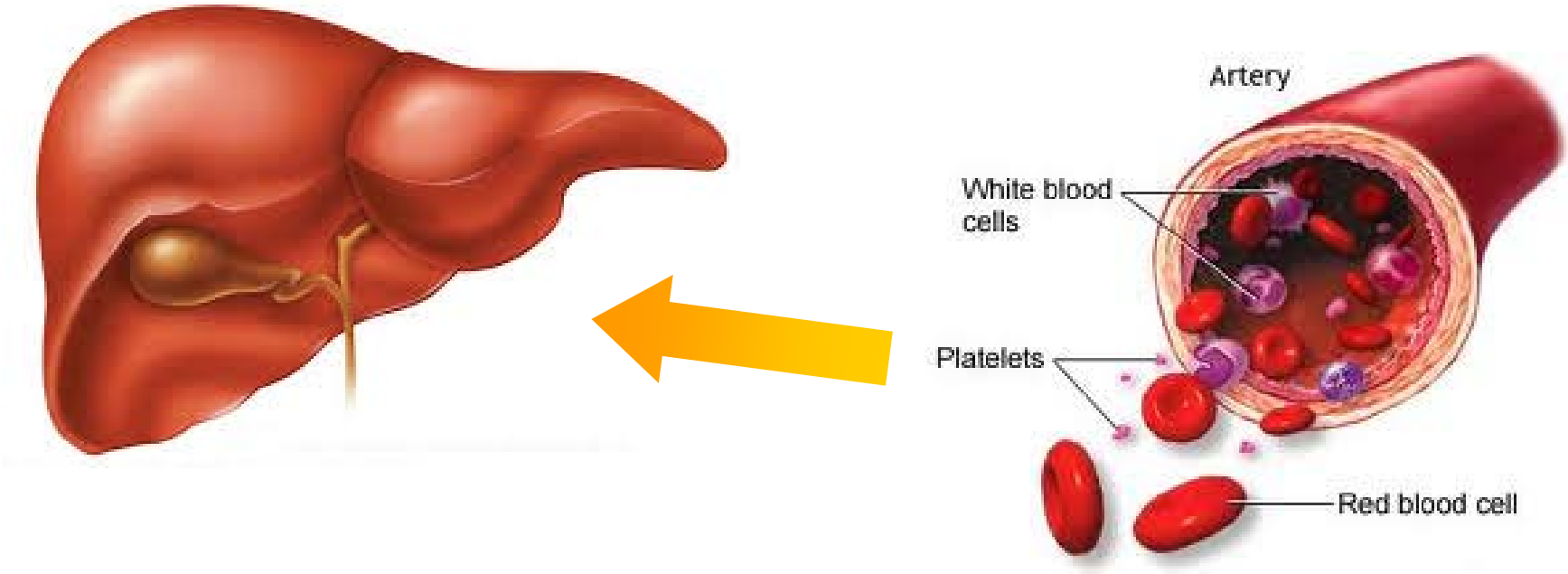
Autoantibodies directed against platelet surface antigens





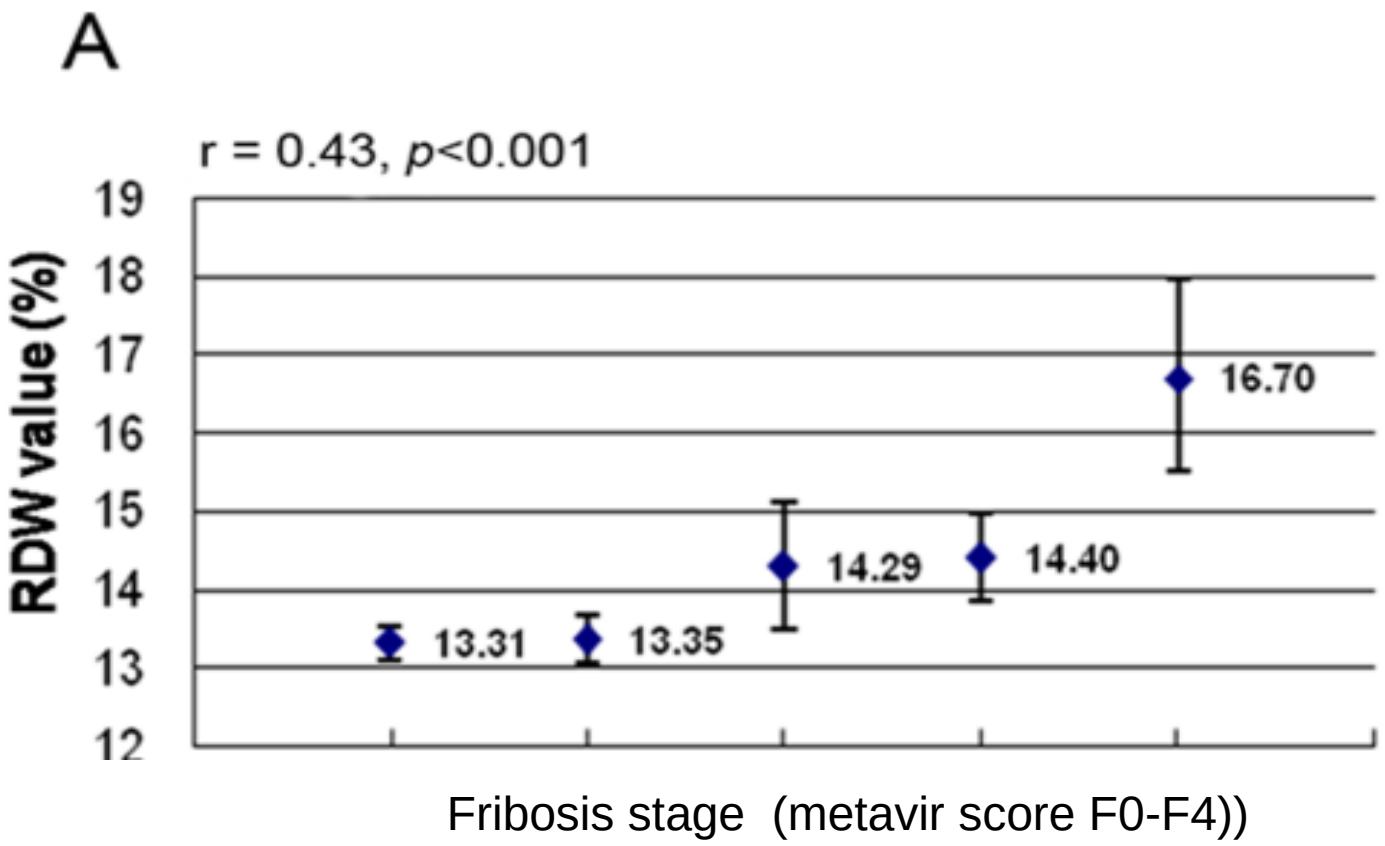
HCV binding thrombocytes generates autoantibodies against the thrombocytes menbrane antigens

Clinical significance of thrombocytopenia In Chronic Liver disease



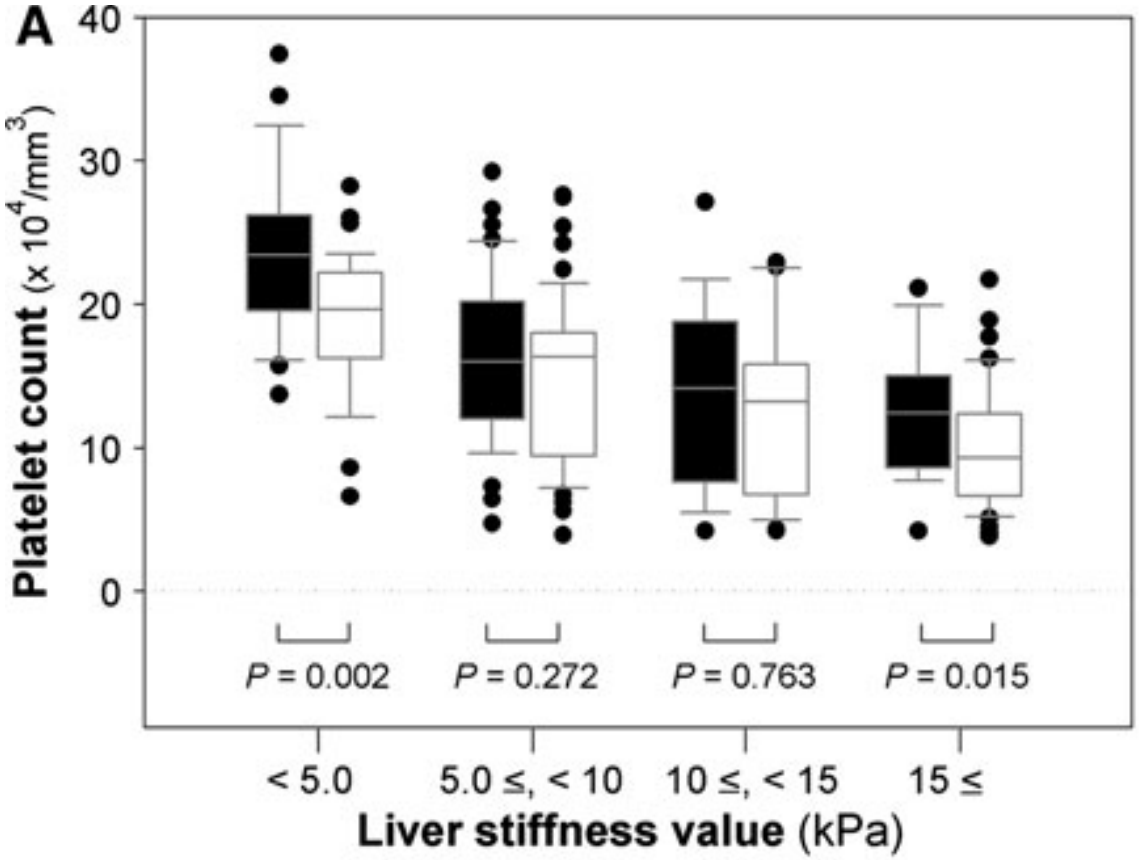
Platelet Count and Fibrosis

N° 458 pt with CHB



Chen B et al PLOs 2013

Comparisons of platelet count following stratification for liver stiffness between patients with chronic liver disease related to HBV (CLD-B) and HCV (CLD-C)



102 patients with CLD-B and 143 patients with CLD-C

Tejima K J Gastroenterol 2010

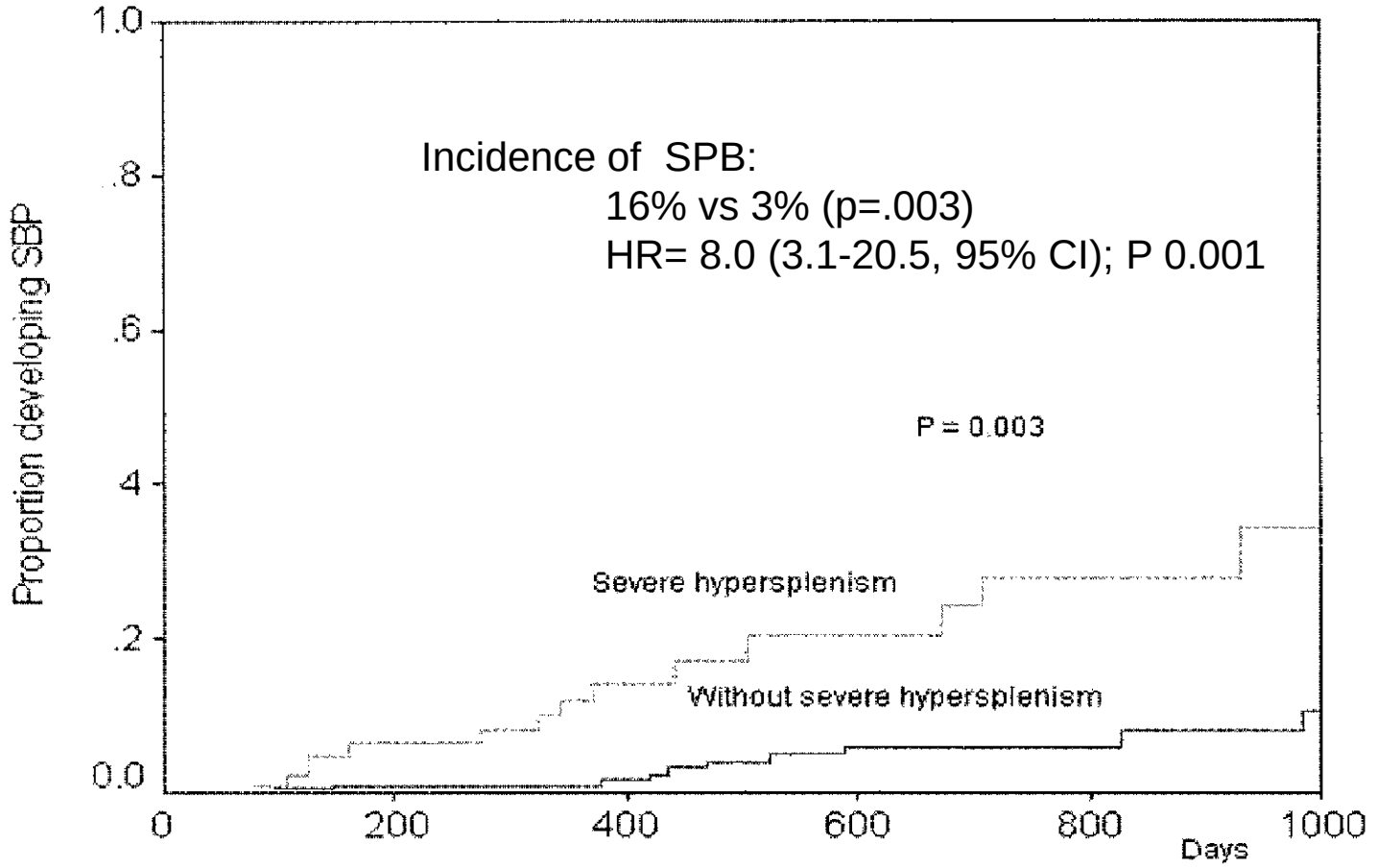
Performance of Noninvasive Methods to Assess Liver Fibrosis in Patients With Viral Chronic Hepatitis C

Score (Original Reference)	Serum Markers/Fibroscan	Etiology	n	≥ F2 (%)	AUC ≥ F2	F4 (%)	AUCF4†
Fibrotest (12)	GGT, haptoglobin, bilirubin, apolipoprotein A1, alpha-2-macroglobulin	HCV	2342	33-74	0.74-0-89	3-25	0.82-0.92
		HBV	218	56-68	0.77-0.85	15-20	0.76-0.87
Forns (11)	Age, GGT, cholesterol, platelets	HCV	1982	32-59	0.75-0.91	3-20	-
		HBV	456	56-74	0.63-0.72	15-26	0.81
APRI (14)	AST platelets	HCV	3160	27-74	0.69-0.88	3-25	0.61-0.94
		HBV	886	56-79	0.72	15-20	0.64-0.76
FIB-4 (13)	Age, ALT, AST platelets	HCV (HIV)	1778	21-36	0.74-0.85	7	0.91
		HBV	776	56-79	0.74-0.86	15-34	0.80-0.93
Hepascore (9)	Age, sex, alpha-2-macroglobulin, hyaluronate, bilirubin, GGT	HCV	1660	39-79	0.74-0.86	6-34	0.80-0.94
Fibrometer (10)	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	HCV	1039	41-56	0.78-0.89	4-15	0.94
		HBV	108	56	0.74	15	0.89
ELF (15)	N-terminal propeptide of collagen type III, hyaluronic acid, TIMP-1, age	HCV/HBV	1346	27-64	0.77-0.87	12-16	0.87-0.90
Fibroscan (19)	Transient elastography	HCV	2052	37-74	0.72-0.91	8-25	0.87-0.98
		HCV-LT	470	36-68	0.81-0.90	9-17	0.87-0.98
		HBV	816	50-68	0.80-0.93	8-25	093-0.96

Martinez et al Hepatology 2011

Hypersplenism and incidence of Spontaneus Bacterial Peritonitis

329 subjects with cirrhosis

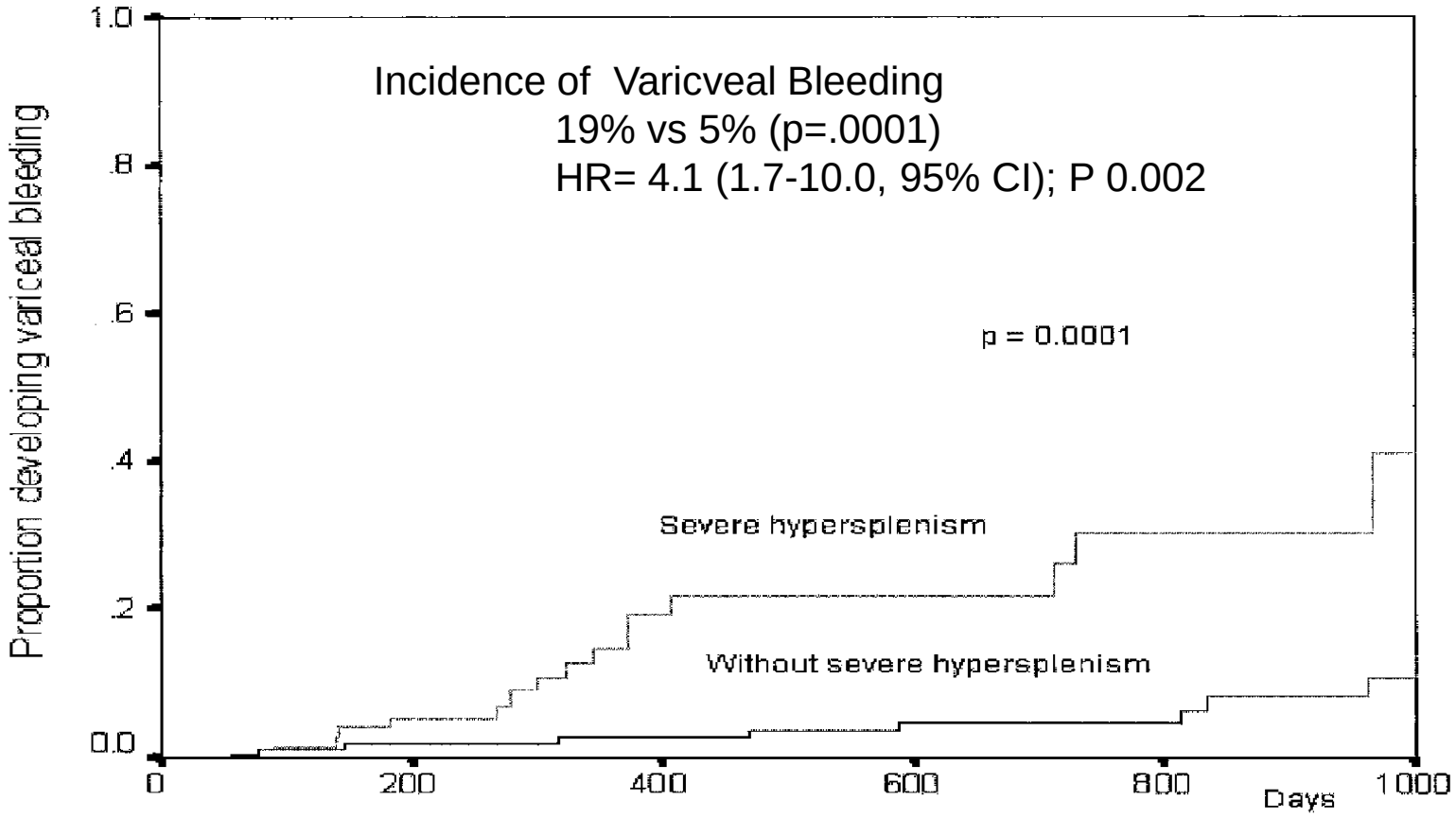


Severe hypersplenism defined as platelet count <75,000/mm^3 and /or WBC<2,000/mm^3

Liangpunnsakul S, et al Am J Med Sci 2003

Hypersplenism and incidence of Oesophageal Varices Bleeding

329 subjects with cirrhosis



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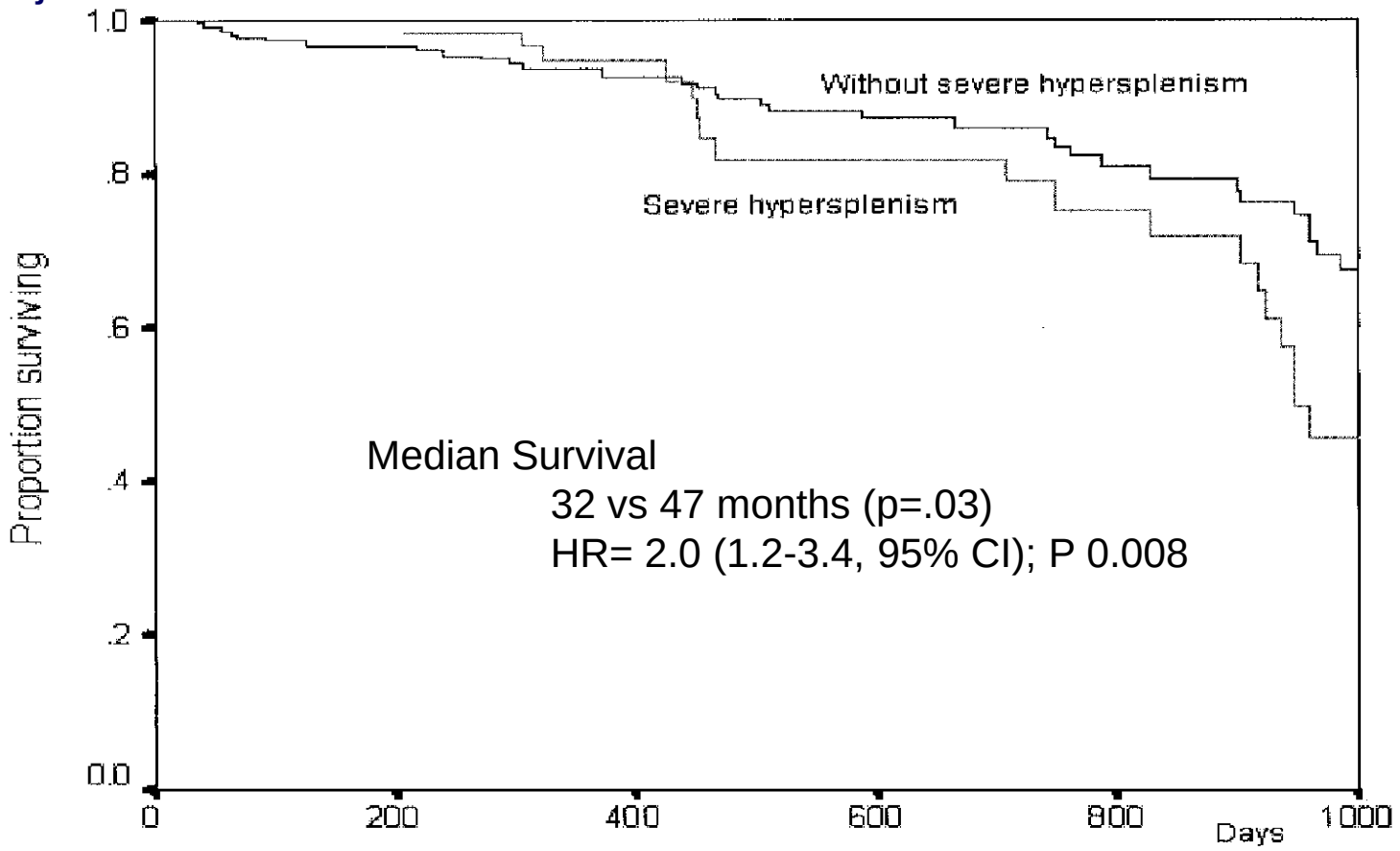
Liangpunnsakul S, et al Am J Med Sci 2003

Hypersplenism and Overall Survival in Advanced Liver disease

329 subjects with cirrhosis



Median Survival

32 vs 47 months (p=.03)

HR= 2.0 (1.2-3.4, 95% CI); P 0.008

Severe hypersplenism defined as platelet count <75,000/mm^3 and /or WBC<2,000/mm^3

Liangpunnsakul S, et al Am J Med Sci 2003

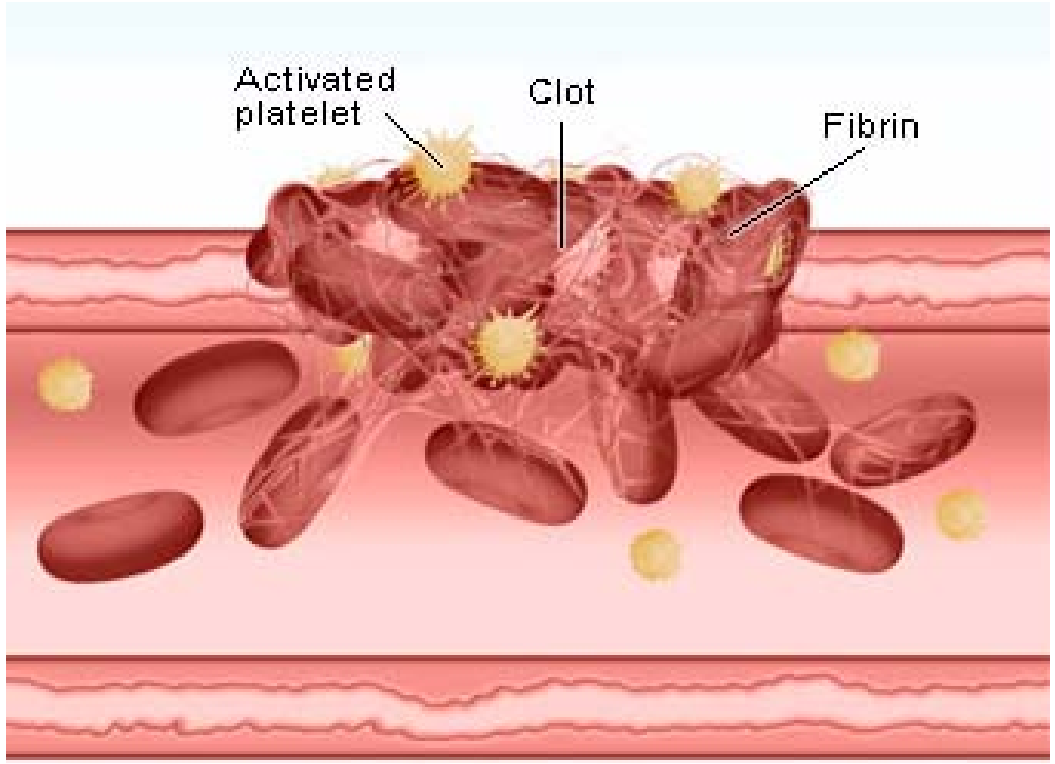
Compensated Cirrhosis: Significant Prognostic Variables for Prediction of Hepatocellular Carcinoma (HCC), Decompensation and Survival in Multivariate Cox Analysis

Outcome	*Variable*	βRegression Coefficient	SE	*P value*
HCC	Age	0.061	0.017	.000
	Bilirubin	1.899	0.715	0.008
	Albumin	-0.064	0.030	0.034
	Viral Status	0.425	0.324	0.189
Decompensation	Platelets	-0.005	0.002	0.024
	Albumin	-0.083	0.023	0.000
	Gammaglobulin	0.043	0.018	0.018
	AST/ALT ratio	1.525	0.486	0.002
	Viral status	-0.523	0.234	0.026
Survival	Age	0.061	0.014	0.000
	Sex	0.627	0.303	0.038
	Platelets	-0.006	0.003	0.018
	Albumin	-0.110	0.024	0.000
	Viral status	0.367	0.271	0.176

Child Pugh Class A n=297 (161 HBV ; 136 HCV). Follow-up 79 months (6-191 months)

Fattovich G et al Am J Gastroeteriol 2002

Platelet and risk of bleeding



Predictors for etiology of UGIB

517 patients with UGIB, 29.8% had variceal and 70.2% non-variceal bleeding

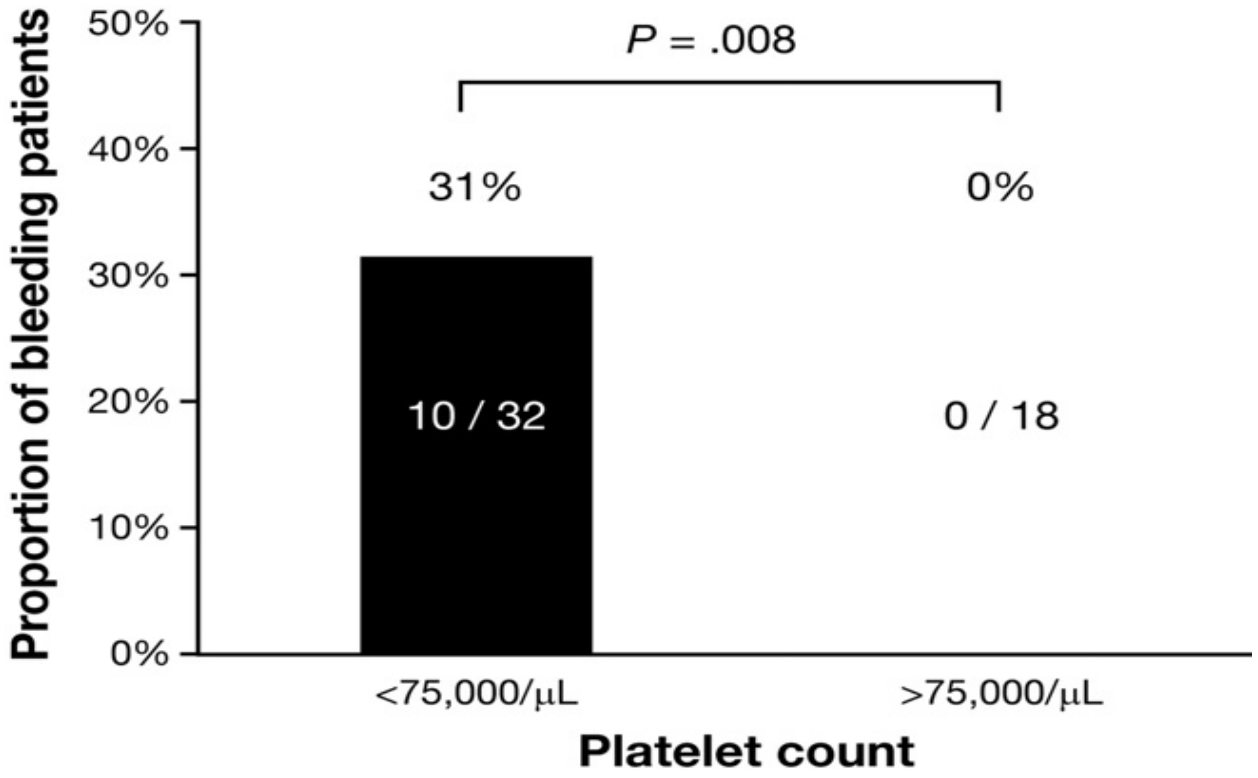
Variable	B	Odds ratio	95% Cl	p
Diagnosis of cirrhosis	2.374	10.74	3.50-32.94	< 0.001
History of variceal UGIB	2.574	13.11	3.09-55.57	< 0.001
Use of NSAIDs	-1.127	0.32	0.13-0.83	0.01
Use of anticoagulant	-3.175	0.04	0.00-0.89	0.04
Ascites	1.483	4.41	1.74-11.16	0.002
Thrombocytopenia	1.019	2.77	1.18-6.50	0.01
High INR	1.561	4.77	1.47-15.42	0.009
High bilirubin	0.886	2.43	1.01-5.84	0.04

UGIB: upper gastrointestinal bleeding;

Matei D J Gastrointestin Liver Dis 2013

Number and proportion of thrombocytopenic patients who had procedure-related bleeding subdivided according to the degree of thrombocytopenia.

N° 50 pt underwent invasive procedure



N° 121 consecutive patients evaluated for OLT

Giannini EG Vlinical gastroenterol and hepatol 2010

Hemostatic Changes in Cirrhosis

Changes imparing hemostasis	Changes promoting hemostasis
Low platelet count Impaired platelet function Low hematocrit, ↑↓ NO production	↑levels of factor VIII and vWF
↓levels of factors II, V, VII, IX, X, XI Quantitative and qualitative abnormalities in fibrinogen	↓levels of protein C, protein S Protein Z, antithrombin, alpha2-macroglobulin, heparin cofactor
↓levels of alpha 2 antiplasmin, TAFI ↑levels of plasma tPA (not balanced by PAI-1 levels)	↓levels of plasminogen

Can not reliably predict the risk of bleeding

Adapted from T . Lisman et al J. Hepatol 2002

How low is too low?

From Hematological point of view

- 150,000 - 50,000: no symptoms
- 50,000 - 20,000: first symptoms
- 20,000-10,000: potentially life-threatening
- <10,000: risk for spontaneous intracranial hemorrhage

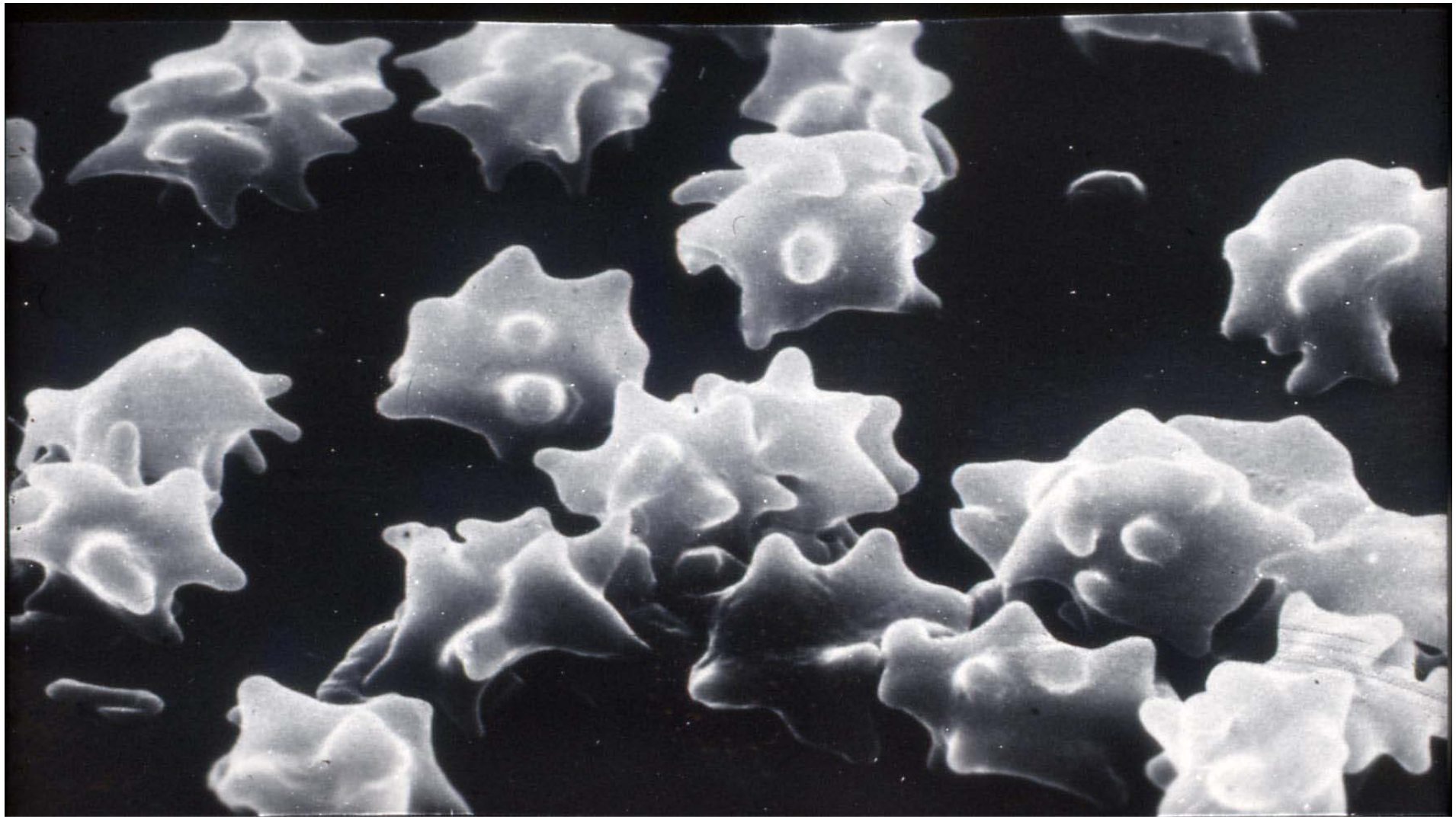
TEG-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy

	TEG Group N (%)	SOC Group N (%)	*P*
Low risk of bleeding			
Paracentesis	12 (40)	7 (23.3)	0.165
Thoracentesis	0	5 (16.7)	0.052
Central Vein Cannulation	1 (3.3)	2 (6.7)	>0.999
TIPSS	0	1 (3.3)	0.313
High risk of bleeding			
Endoscopic variceal banding	6 (20)	4 (13.3)	0.730
Hepatic Resection	3 (10)	2 (6.7)	>0.999
Other abdominal surgery	2 (6.7)	2 (6.7)	>0.999
Radio Frequency Ablation	2 (6.7)	1 (3.3)	>0.999
Endoscopic polipectomy	3 (10)	0	0.119
Percutaneous Liver Biopsy	0	3 (10)	0.237
Biopsy of other sites	0	1 (3.3)	0.313
Drainage other sites	0	1 (3.3)	0.313
ERCP with Sphincterotomy	0	1 (3.3)	0.313
Thoracotomy	1 (3.3)	0	0.313

all subjects in the SOC group received blood product transfusions versus 5 in the TEG group

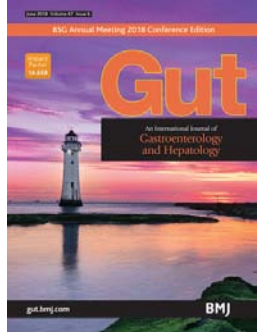
De Pietri L. Hepatology 2015

Pitted cells

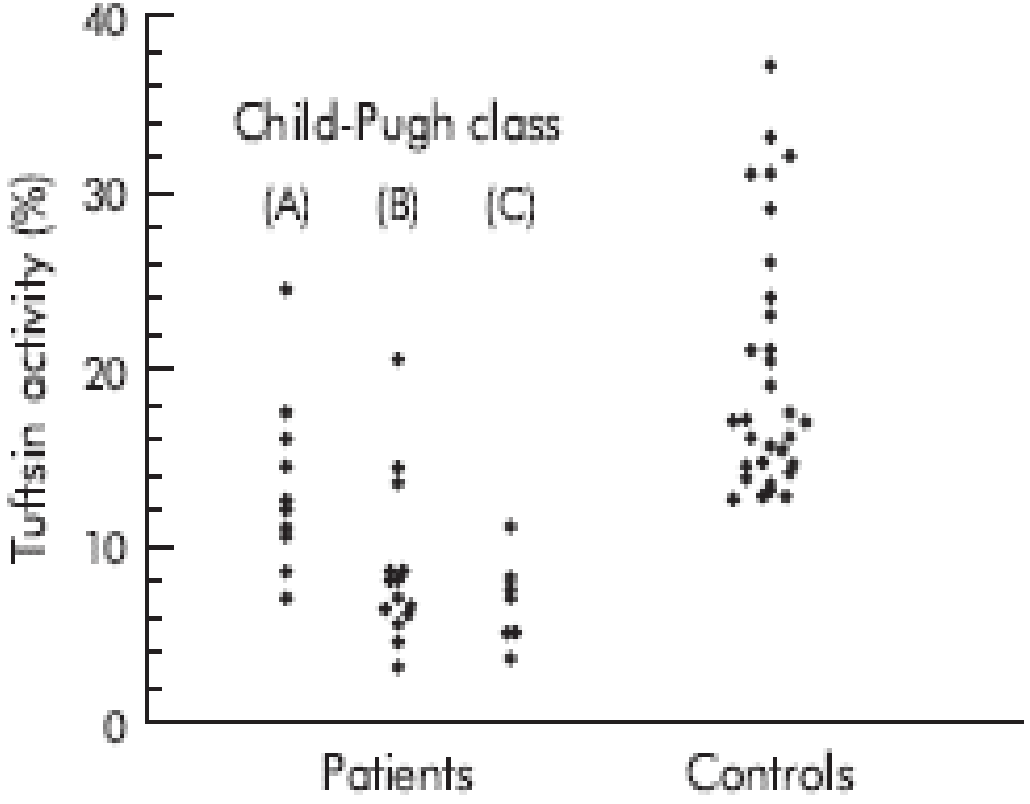


Impaired tuftsin activity in cirrhosis: relationship with splenic function and clinical outcome

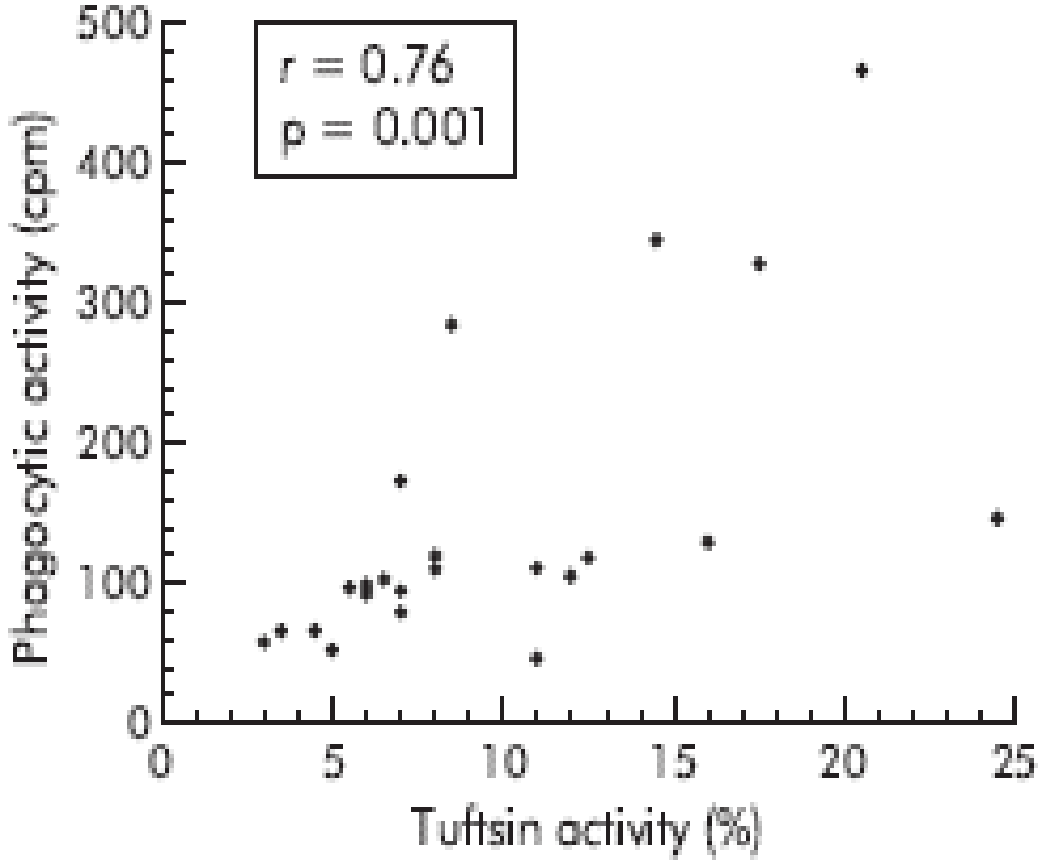
F Trevisani, E Castelli, F G Foschi, M Parazza, E Loggi, M Bertelli, C Melotti, M Domenicali, G Zoli, M Bernardi *Gut* 2002;**50**:707–712



serum tuftsin activity in patients with cirrhosis and in healthy controls.



Correlation between patient tuftsin activity and neutrophil granulocyte phagocytic activity



- ✓Manifestazioni ematologiche in corso di malattie epatiche
- ✓Manifestazioni ematologiche maligne del fegato
- ✓Disordini vascolari del fegato
- ✓Sinusoidal obstructive syndrome (SOS)/Veno Occlusive disease (VOD)
- ✓GVDH
- ✓Riattivazione Virale in corso di Chemioterapia /mAb

Hematologic Malignancies and Liver

- **The incidence of hematologic malignancies and their extranodal manifestations is continuously increasing.**

- **The imaging features of more common hepatic diseases such as hepatocellular carcinoma, metastases, and infection may overlap**

- **Unsuspected Hepatic involvment can be seen**
  - **Primary and secondary Hepatic Lymphoma**
  - **Post-transplant lymphoproliferative disorder**
  - **Myeloid sarcoma (chloroma)**
  - **Multiple myeloma**
  - **Castleman disease (giant lymph node hyperplasia)**
  - **Lymphohistiocytosis**

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Hematologic Malignancies and Liver

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Hematologic Malignancies and Liver

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Primary Hepatic Lymphoma (PHL)

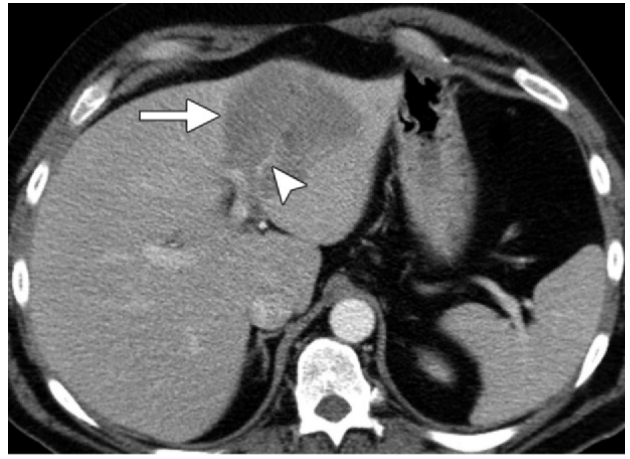
- ✓Symptoms mainly caused by liver involvment at the presentation
- ✓Absence of distant limphoadenopathies, palpable cinically at the presentation or detected during staging radiological studies
- ✓Absence of a leukemic bloood profile

Lei et al Leuk Lymph 1998

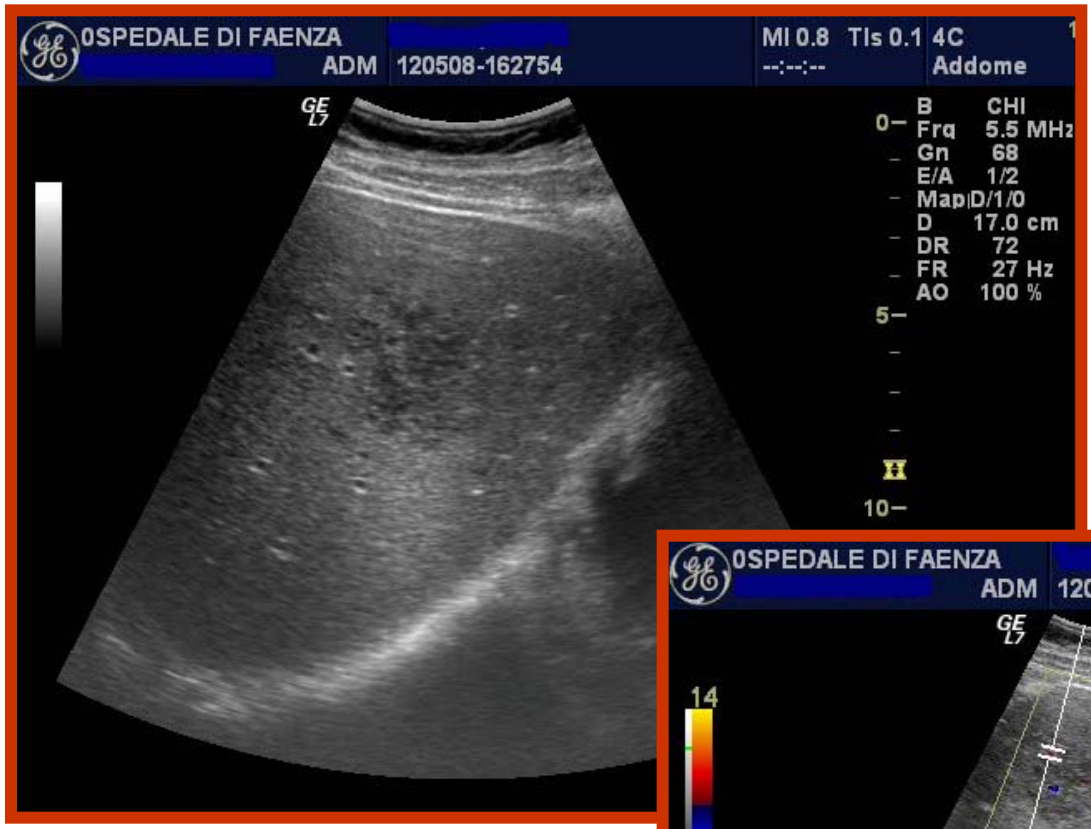
Primary Hepatic Lymphoma (PHL)

- ✓**0.016% NH**
- ✓**>Prevalence in HCV**
- ✓**Other: HBV, EBV, HIV,**
- ✓**Risk factor for lymphoproliferative disorders (Sjogren sd)**
- ✓**Most cases of PHL are of B-cell lineage (95%)**
- ✓**Solitari and well defined tumor (60%)**
- ✓**Multiple nodule (35-40%)**
- ✓**Diffuse infiltrative form (uncommon in PHL and indicates a poor prognosis)**

Primary Hepatic Lymphoma (PHL)



- ✓Ultrasound usually Hypoecoic lesion
- ✓DD: Hepatocelular Carcinoma (HCC) Cholangiocarcinoma (CCC) Metastases, fungal microabscesses
- ✓A multiphase CT study is not indicated for diagnosis of hepatic lymphoma because the lesions typically are hypo- vascular in all phases.
- ✓Diffusion- weighted MR imaging is an important component of the imaging protocol for characterization of suspected lymphomatous lesions (15%)
- ✓In Patients with cirrhosis HCC/PHL may be infiltrative and the hypo-vascular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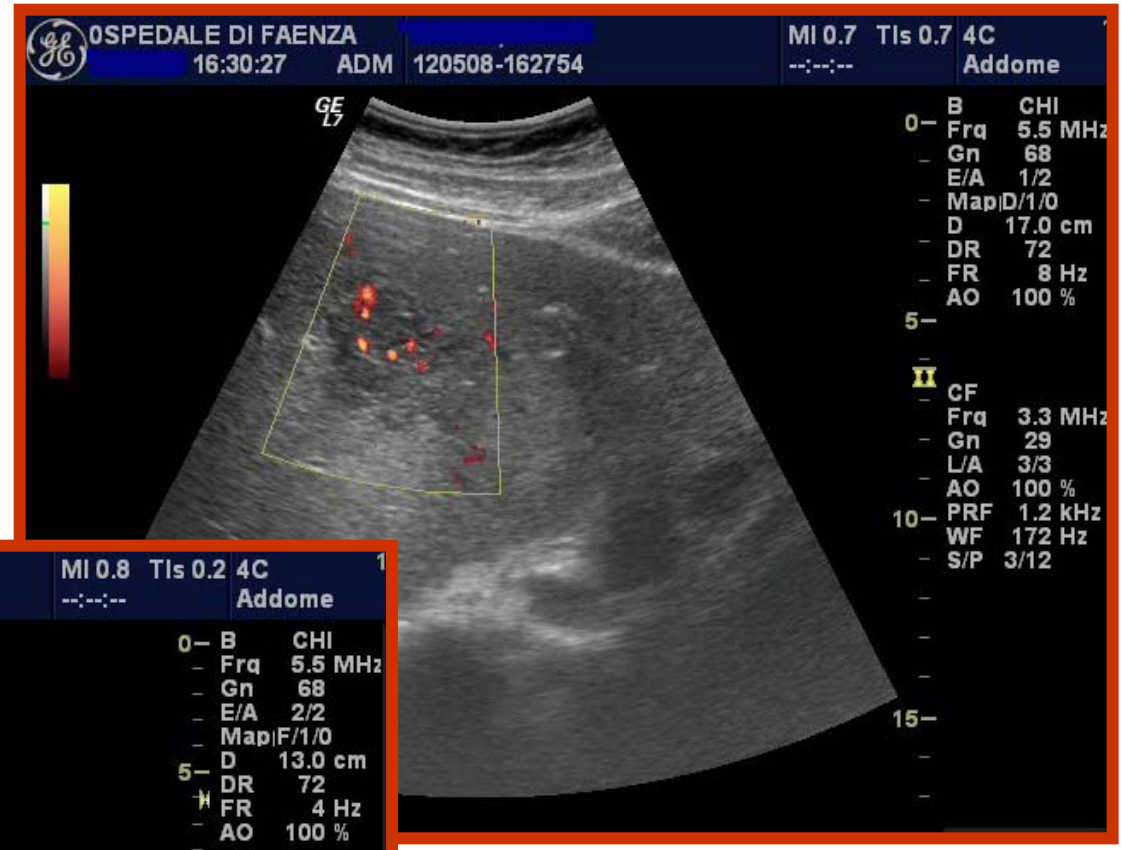
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WF 172 Hz
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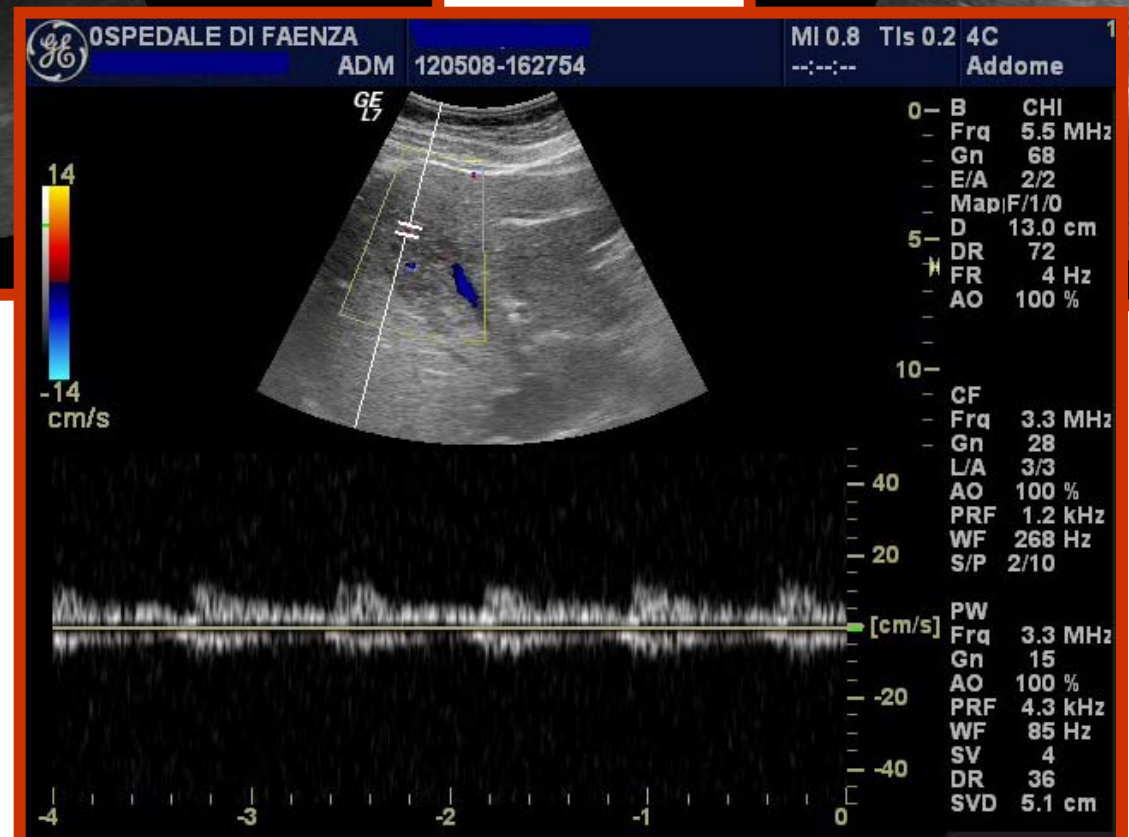
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Gn 15
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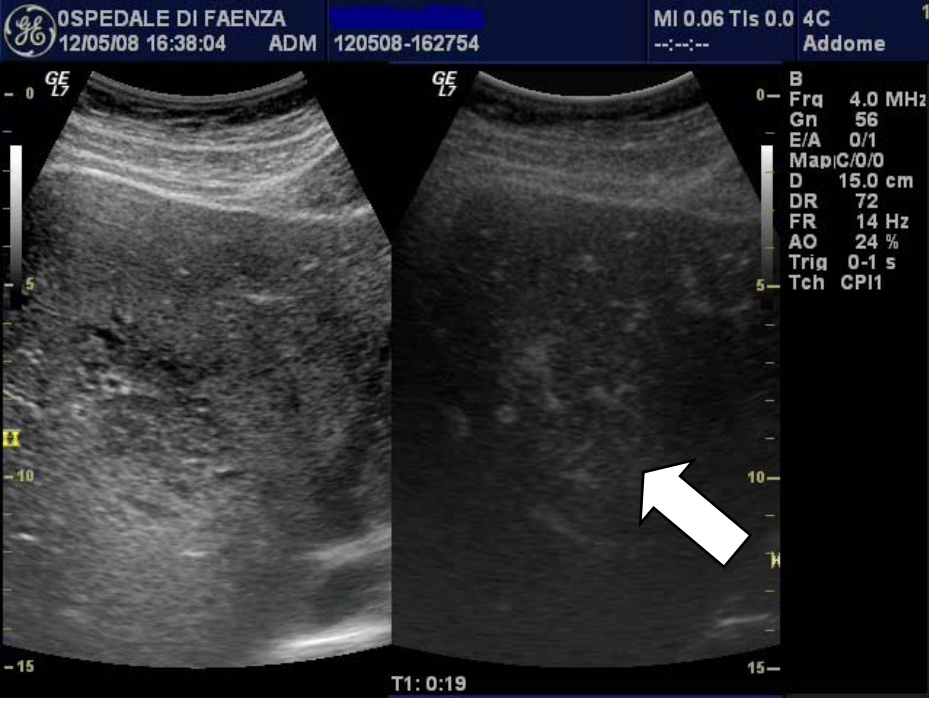
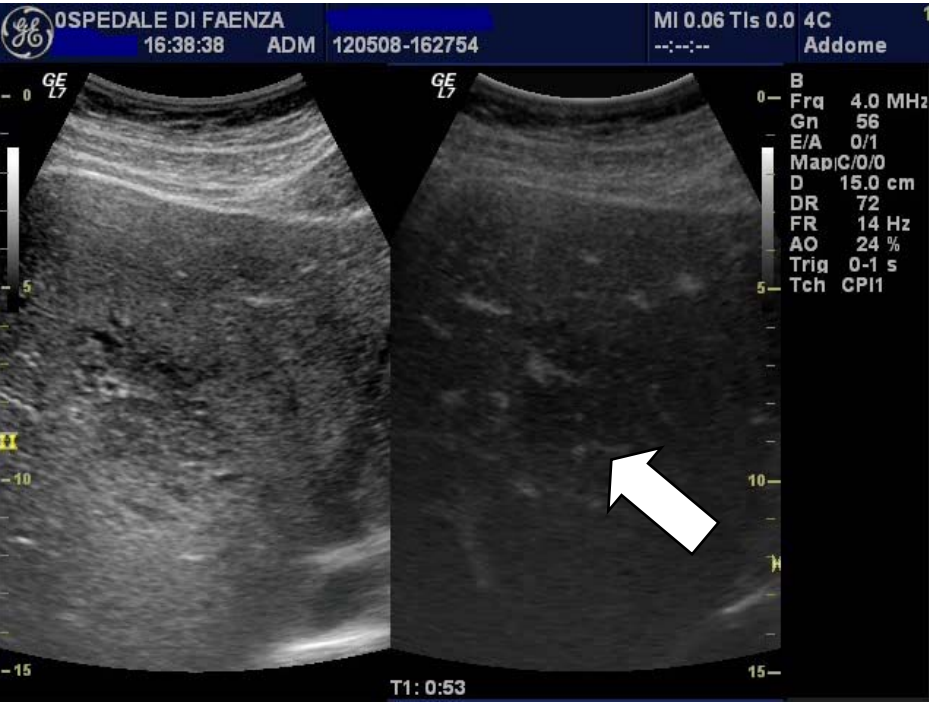
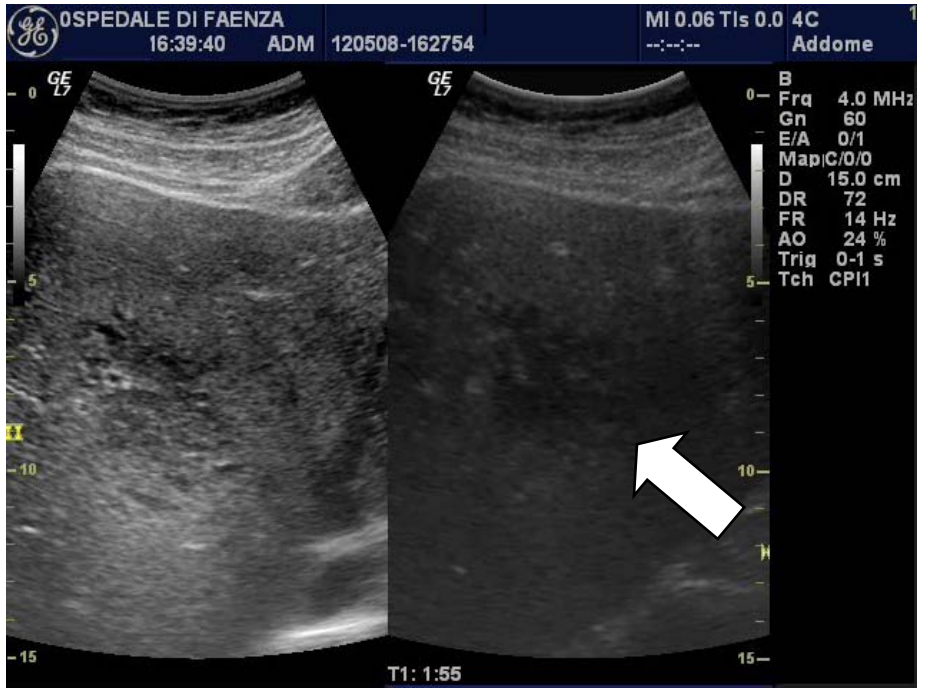
Role of Contrast-Enhanced Ultrasonography in Primary Hepatic Limphoma



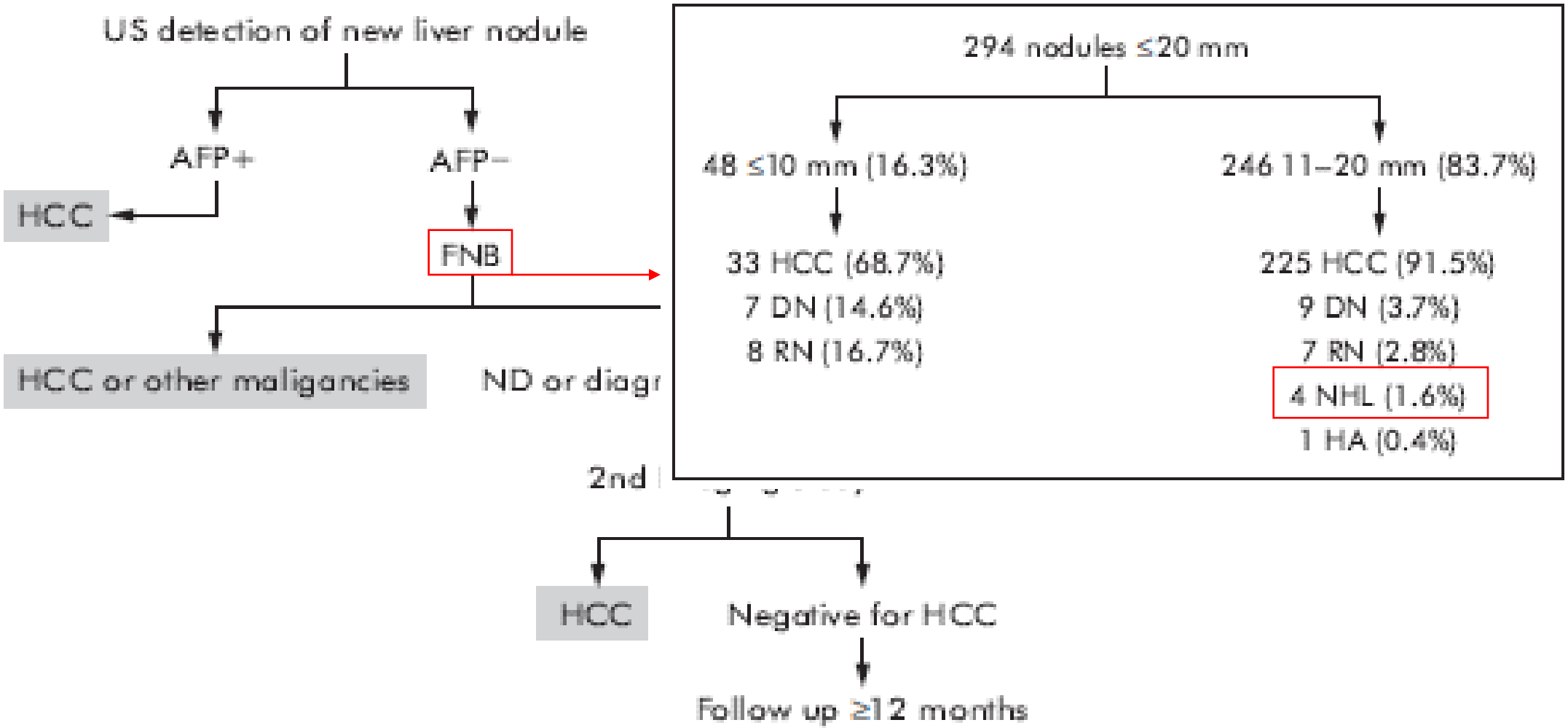




Although no imaging pattern on CEUS is specific for PHL, the scarce marginal definition and irregularity of the lesion on ultrasonography may represent a finding warranting focal biopsy.

Foschi et al 2010

Ultrasound guided fine needle biopsy of early hepatocellular carcinoma complicating liver cirrhosis: a multicentre study



Caturelli E et al Gut 2004

CEUS LI-RADS

Liver Imaging Reporting and Data System 2015.v1

LI-RADS Algorithm **RULES of UTILIZATION**

1. As with CT and MRI LI-RADS categorization, the CEUS LI-RADS algorithm imposes a **categorization order**:

2. first, CEUS LR inadequate (due to technical or other factors), LR-treated, LR-1 (definitely benign observations or nodules) and LR-5V (If there is definite tumor within vein even if a parenchymal nodule is not identified).

3. If no nodule is seen on pre contrast ultrasound, no categories will be assigned at this point.

4. Only observations with visible nodules on pre contrast ultrasound will be further categorized with CEUS.

5 LR-M will be assigned next (features that favor non-HCC malignancy).

6 Observations with visible nodules on pre contrast ultrasound will then be assigned categories of CEUS LR-2, -3, -4, or -5 as appropriate

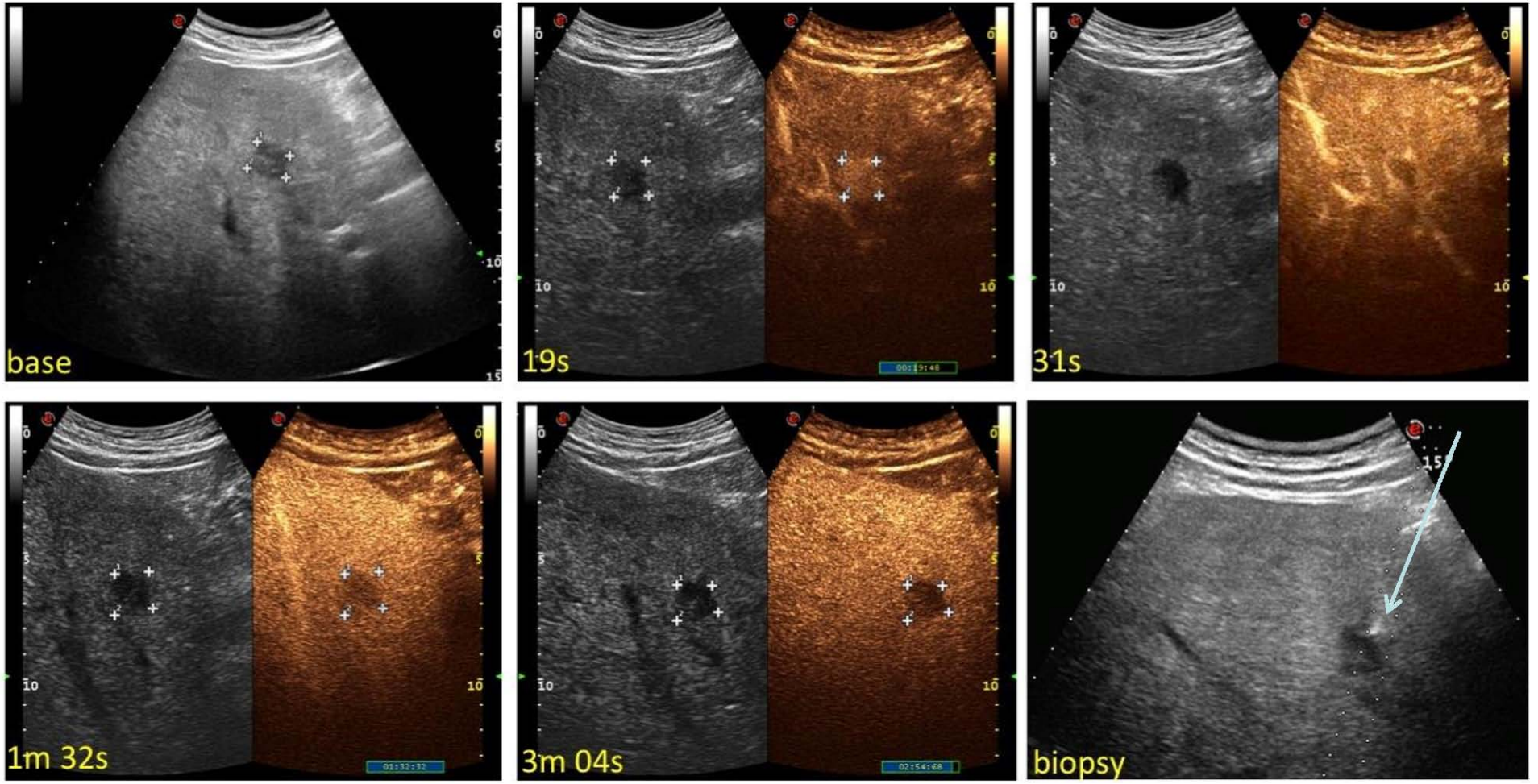
CEUS LI-RADS

Liver Imaging Reporting and Data System 2015.v1

LI-RADS Category	Concept and Definition
LR-1 **Definitely Benign**	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2 **Probably Benign**	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3 **Intermediate probability for HCC**	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4 **Probably HCC**	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5 **Definitely HCC**	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V **Definitely HCC with Tumor in Vein**	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M **Probable malignancy, not specific for HCC**	**Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC. **Definition:** Observation with one or more imaging features that favor non-HCC malignancy.
LR-Treated **Treated Observation**	**Concept:** Loco-regionally treated observation. **Definition:** Observation that has undergone loco-regional treatment

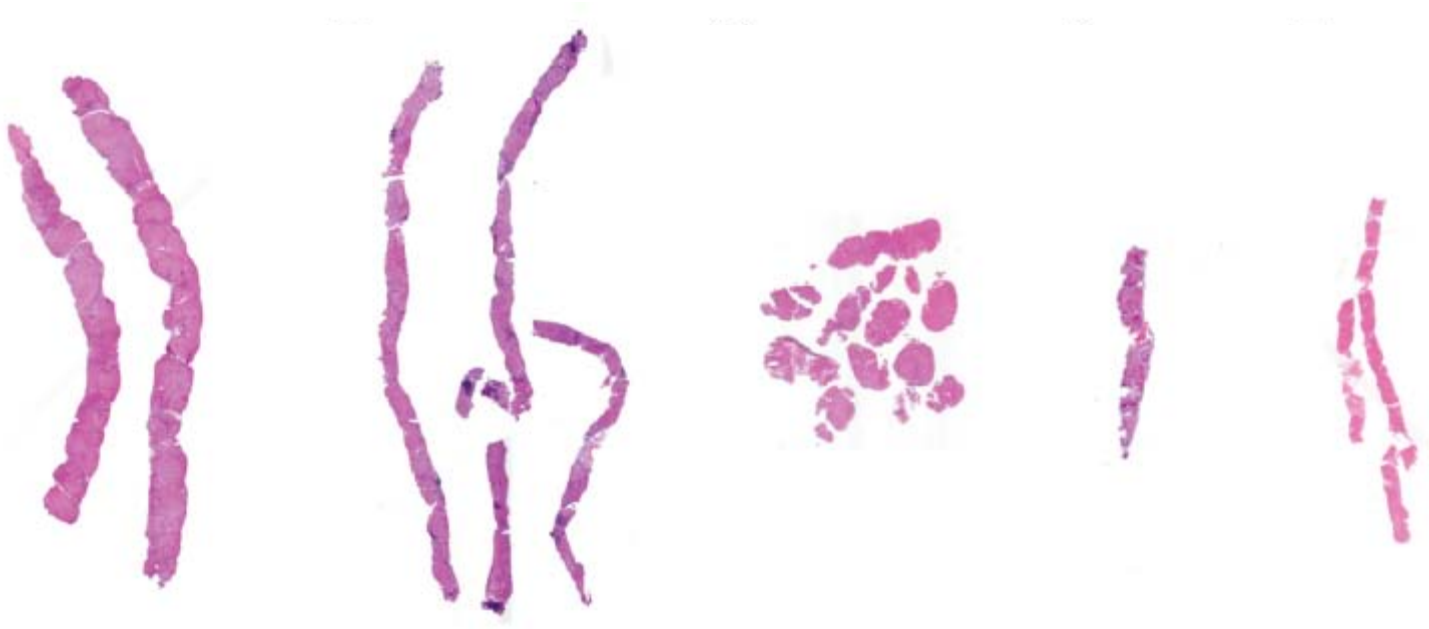
CEUS LI-RADS scheme v2015

CEUS LR-M: Probably Malignant, not specific for HCC



Cholangiocarcinoma

Biopsia epatica



16 G (tot 2.7 cm)
Cutting needle
2 passes

18 G (tot 4.8 cm)
Cutting needle
3 passes

16 G (1.1 cm)
Suction needle

18 G
(0.5 cm)

20 G
(1.5 cm)

Malignancy → smaller than 18G → ok
Diffuse → smaller than 18G → error 2/3 Pt

AASLD Position Paper Rockey DG et al Hepatology 2009

Hematologic Malignancies and Liver

- ✓Primary and secondary Hepatic Lymphoma
- ✓Post-transplant lymphoproliferative disorder
- ✓Myeloid sarcoma (chloroma)
- ✓Multiple myeloma
- ✓Castleman disease (giant lymph node hyperplasia)
- ✓Lymphohistiocytosis

Post-transplant Lymphoproliferative Disorder (PTLD)

- **Increasing incidence related to growing numbers of transplantations**

- **PTLD:**
  - **kidney transplants (0.8 to 2.5%)**
  - **pancreatic transplants (0.5 to 5.0%),**
  - **liver transplants (1.0 to 5.5%),**
  - **heart transplants (2.0 to 8.0%),**
  - **lung transplants (3.0 to 10.0%),**
  - **multiorgan and intestinal transplants (≤20%).**

- **incidence depends on the degree of HLA matching and the need for T-cell depletion protocols before transplantation**

Tomasian A et al RG 2015

Post-transplant Lymphoproliferative Disorder (PTLD)

- **EBV seronegativity before transplantation in solid-organ transplant recipients is an important predisposing factor of PTLD**
- **Epstein-Barr virus infection has been linked to 85% of PTLD cases**
- **Bimodal curve, with an initial spike (mostly involving EBV-positive transplant recipients) during the first year; late spike (often involving EBV-negative recipients), which typically occurs 5 to 15 years after transplantation.**
- **Involved abdominal organ**
  - **Liver (50%),**
  - **Small bowel (25%)**
  - **kidneys (17%)**

Tomasian A et al RG 2015

Classification of Post-Transplantation Lymphoproliferative Disorder (PTLD) by the World Health Organization (WHO).

EBV positive lymphoid infiltration consists of a group of different diseases

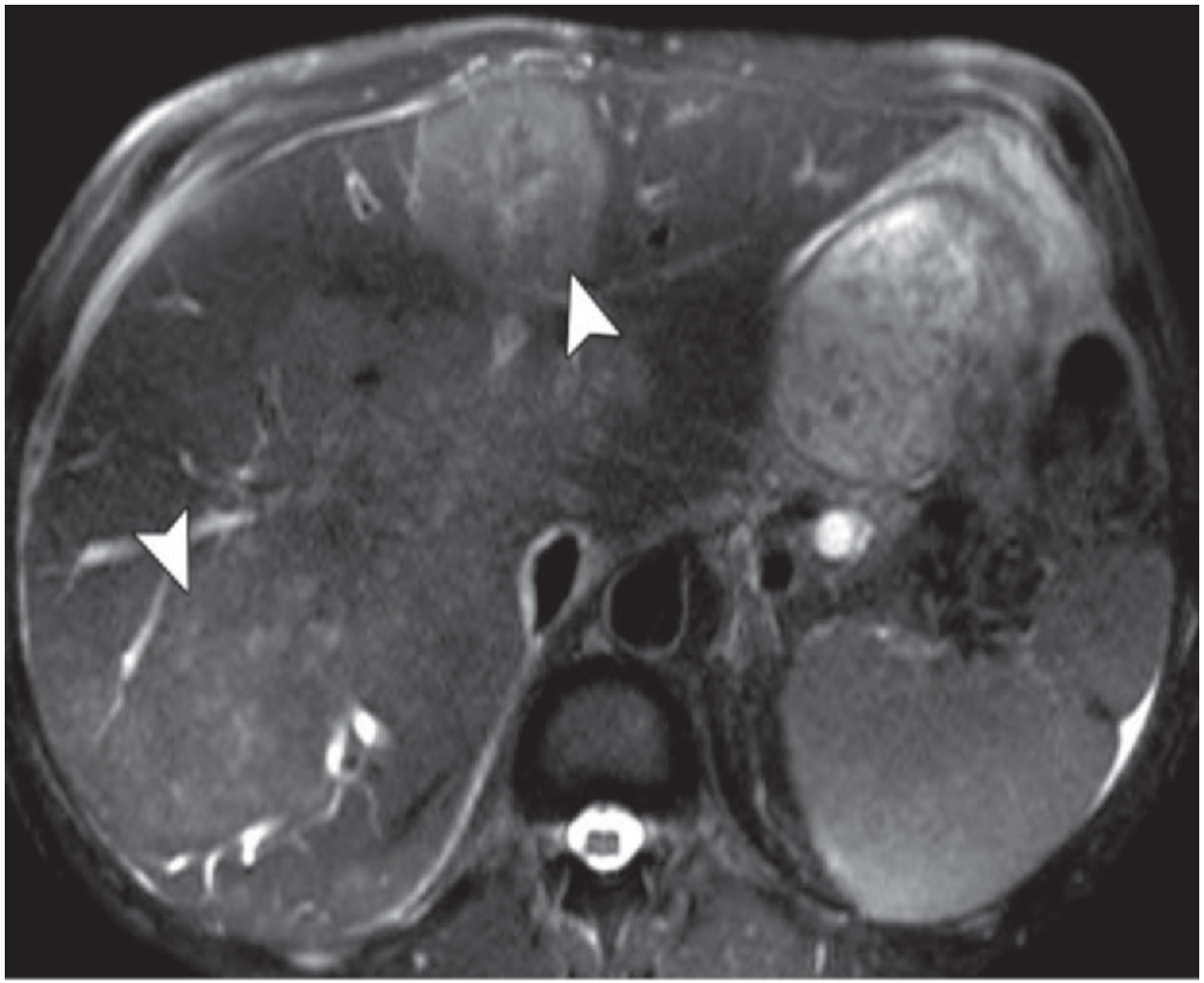
Characteristic	Nondestructive PTLD†	Polymorphic PTLD	Monomorphic PTLD	Hodgkin's Lymphoma–like PTLD
Underlying architecture	Nondestructive	Destructive	Destructive	Destructive
Composition	Plasma cells, small lymphocytes, immunoblasts	Complete spectrum of B-cell maturation	Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD	Fulfills specific criteria for classic Hodgkin's lymphoma
Immunohistochemical features	No diagnostic value	Mixture of B cells and T cells	Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type)	CD20–, CD30+; most cases CD15+
EBV association	Almost 100%	>90%	Both EBV-positive and EBV-negative	>90%
Clonality	No in most cases	Variable	Yes	Yes
Molecular genetic findings	None	Variable (BCL6 somatic hypermutations)	Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients)	No information available
Clinical features	Mostly early PTLD	Variable	Both early and late PTLD	Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT

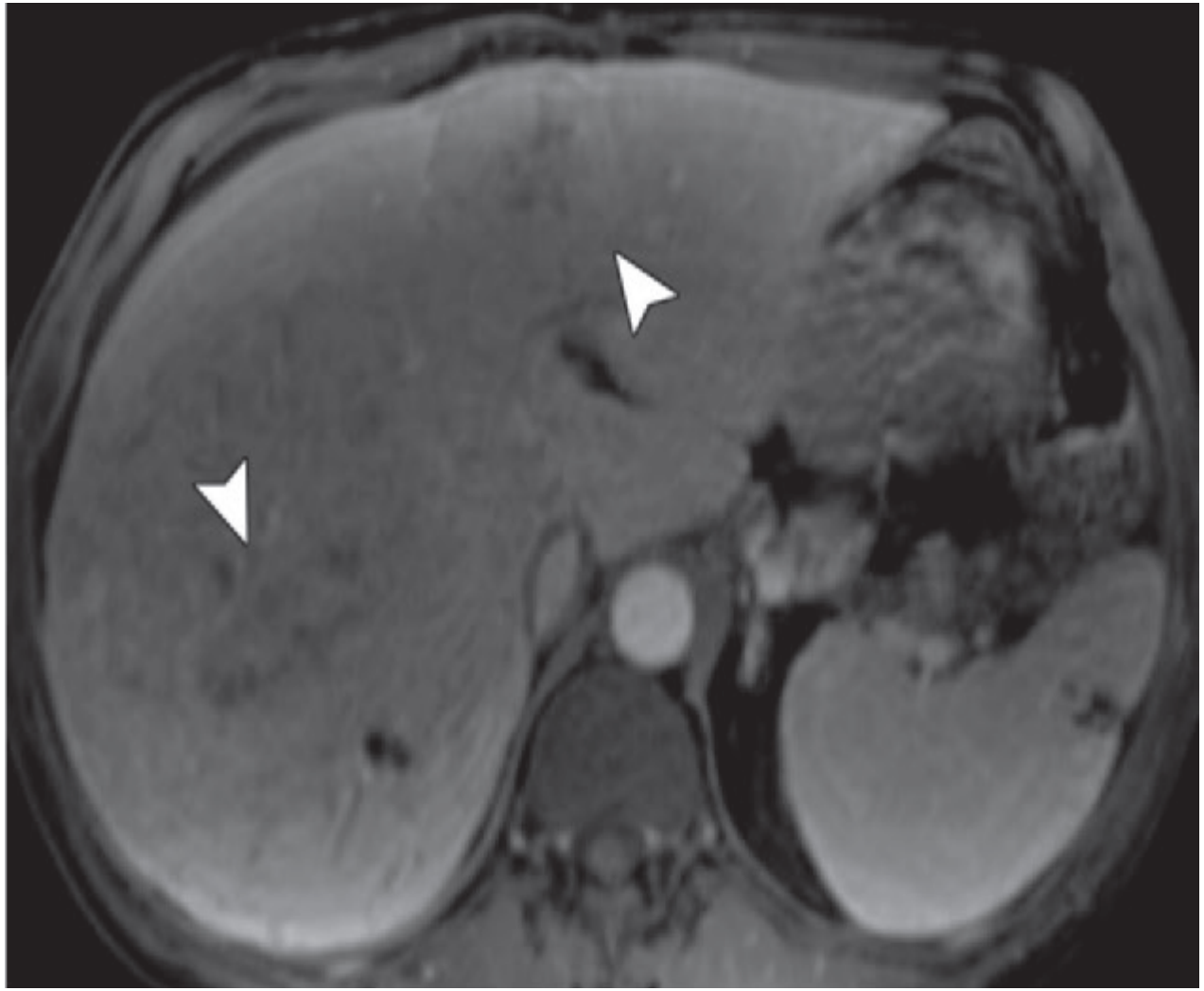
Longo TD NEJM 2018

PTLD in a 56-year-old man with elevated liver function test results 6 months after kidney transplant

Axial T2-weighted MR image shows hyperintense hepatic masses

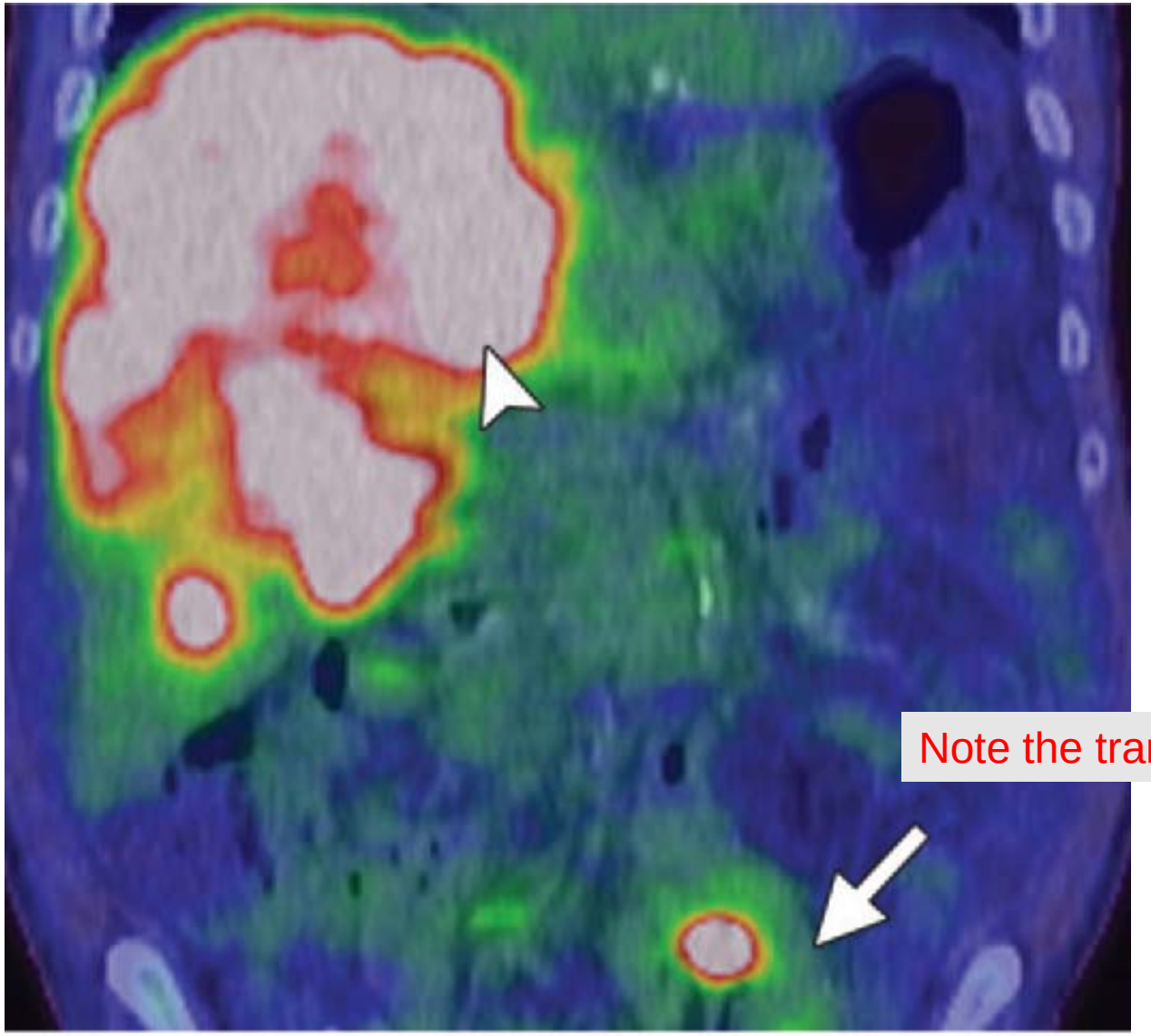
Axial contrast-enhanced venous phase MR image shows barely visible lesions





Tomasian A et al RG 2015

Coronal fused FDG PET/CT image shows the lesions as avidly hypermetabolic



Note the transplanted kidney

Hematologic Malignancies and Liver

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Myeloid sarcoma (granulocytic sarcoma or chloroma)

- Rare extramedullary proliferation of immature myeloid cells.
- Most commonly in patients with AML (3%–5% of these patients) .
- Increasing probably intensive chemotherapy and bone marrow transplant.
- Associated with other myeloproliferative conditions (chronic myeloid leukemia, myelodysplastic syndrome, essential thrombocythemia and polycythemia vera).
- Myeloid sarcoma may manifest during remission remission of a hematologic malignancy in up to 20%
- The most common sites are the bones, lymph nodes, soft tissues, skin, and breasts.
- The imaging features of hepatic myeloid sarcoma are nonspecific and are similar to those of hepatic lymphoma

Tomasian A et al RG 2015

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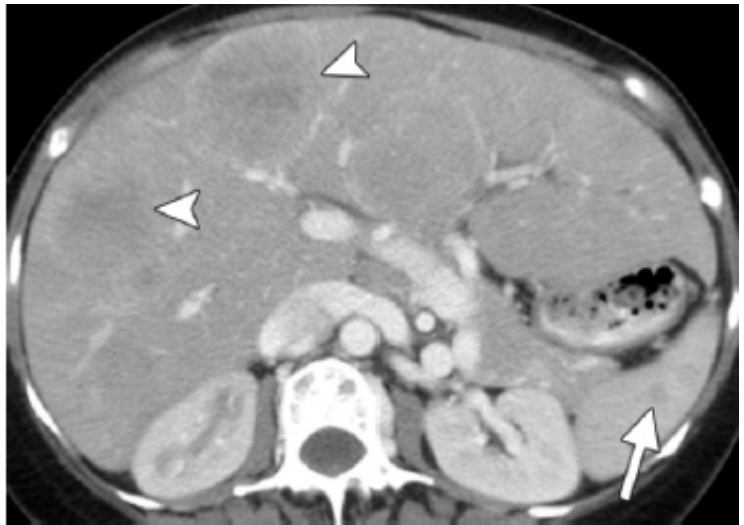
Multiple myeloma

- **Extraosseous myeloma was once thought to be rare, but autopsy series have shown extraosseous disease in up to 64% of patients with myeloma**
- **The lymph nodes, pleura, and liver are the most commonly involved organs.**
- **Extraosseous involvement is associated with a poorer prognosis.**
- **Hepatic involvement may be unifocal, multifocal, or diffuse.**
- **Liver involvement may be asymptomatic or may manifest as hepatomegaly, jaundice, ascites, or fulminant liver failure.**
- **Liver dysfunction in a patient with multiple myeloma can result from plasma cell infiltration or amyloidosis, and pathologic confirmation is often required.**

Tomasian A et al RG 2015

Multiple myeloma

- Focal hepatic lesions are often hypoechoic at US. Rarely hyperechoic or mixed echogenicity;
- At CT Focal hepatic lesions are typically hypoattenuating, without calcification or substantial contrast enhancement Biliary obstruction may occur.
- At MR Myelomatous lesions are usually hyperintense on T1-weighted and T2-weighted. Hyperintensity on T1-weighted images is presumably due to the high concentration of light chain protein in the lesions,



Extraosseous myeloma in a 37-year-old woman with bone lesions. Axial CT image obtained to locate a possible primary malignancy shows multiple solid lesions in the liver (arrowheads) and spleen (arrow). The lesions are mildly hypoenhancing and do not show calcification.

Tomasian A et al RG 2015

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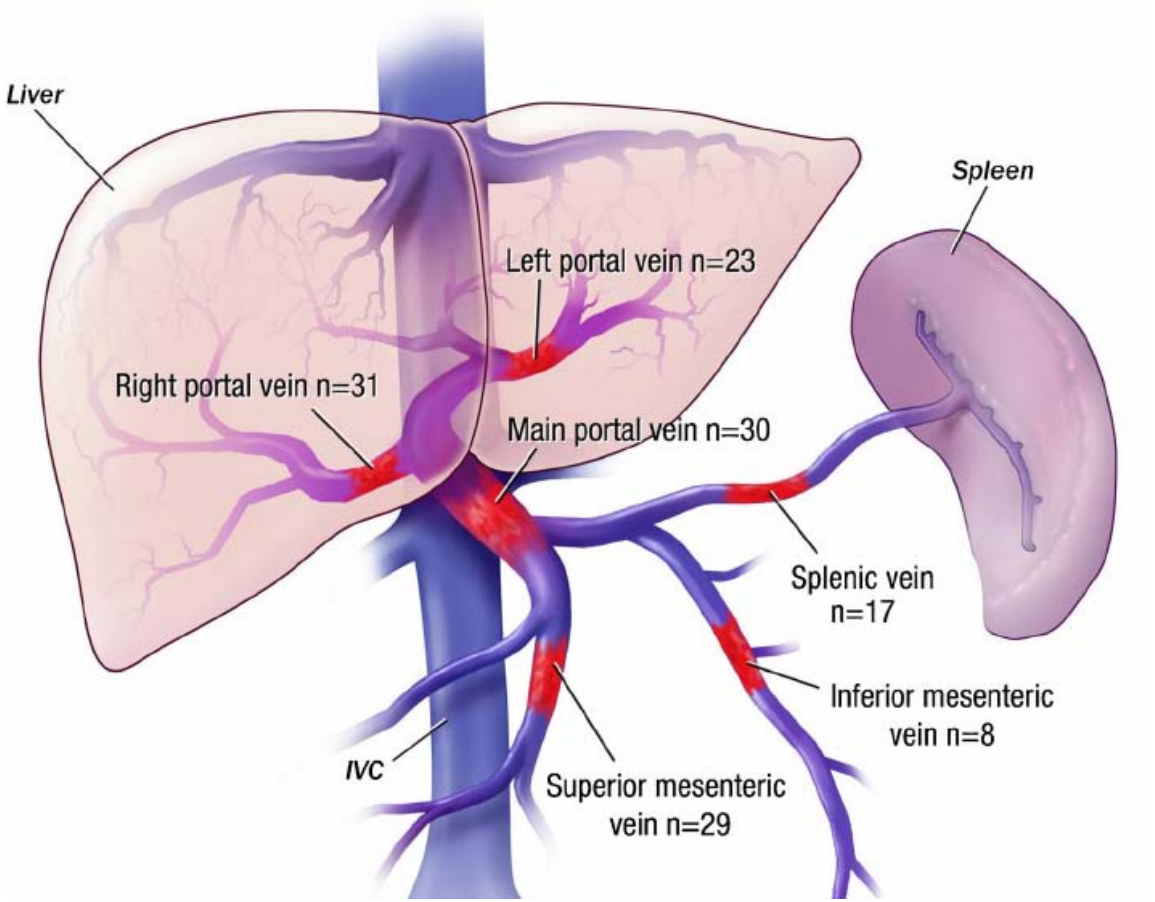
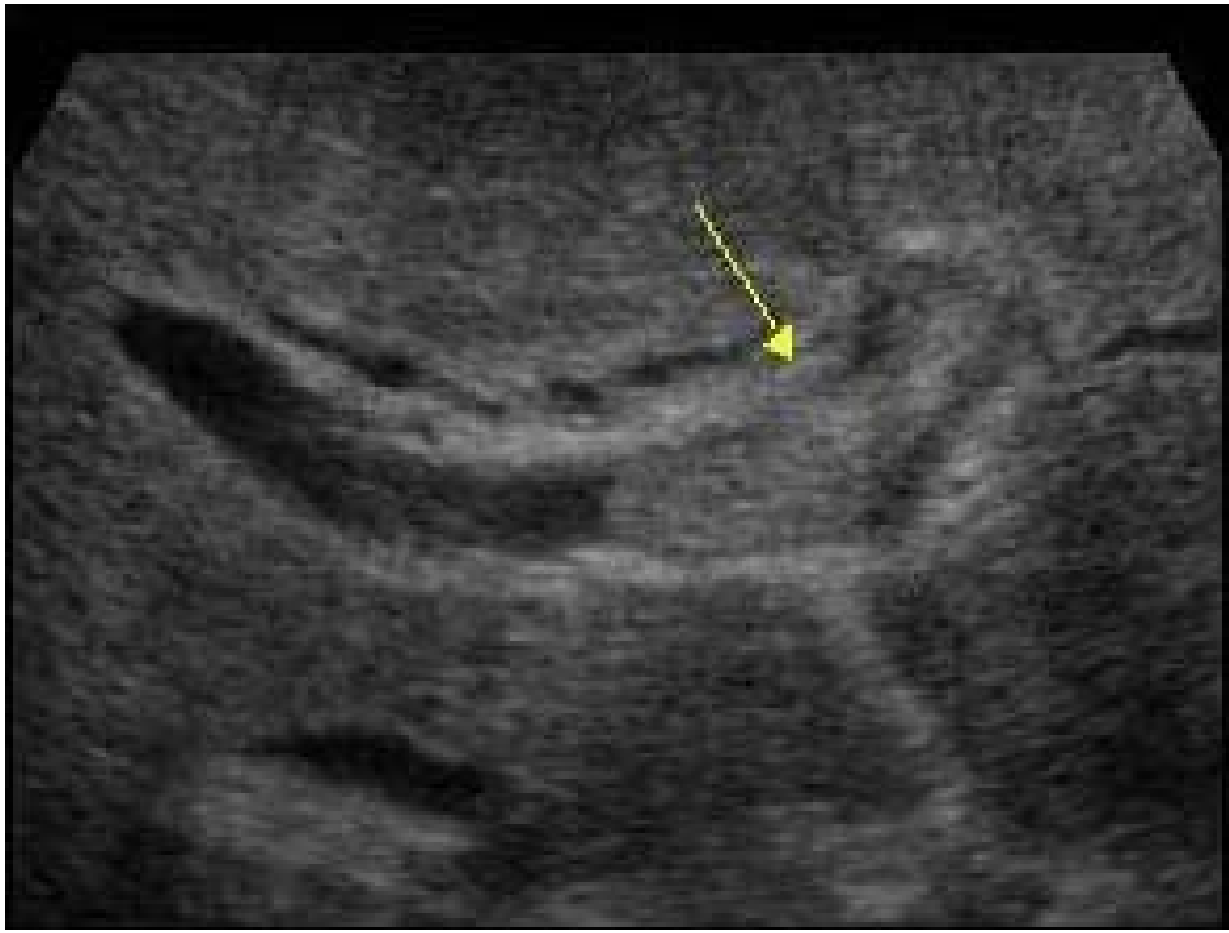
Vascular Liver Disease

1. Splanchnic vein thrombosis in patients without underlying liver disease
2. Budd–Chiari syndrome
3. Acute portal vein thrombosis (non-cirrhotic, non-malignant)
4. Extrahepatic portal vein obstruction (non-cirrhotic, non-malignant)
5. Idiopathic non-cirrhotic portal hypertension
6. Hepatic vascular malformations in hereditary haemorrhagic telangiectasia
7. Sinusoidal obstruction syndrome
8. Cirrhosis as a prothrombotic condition: portal vein obstruction

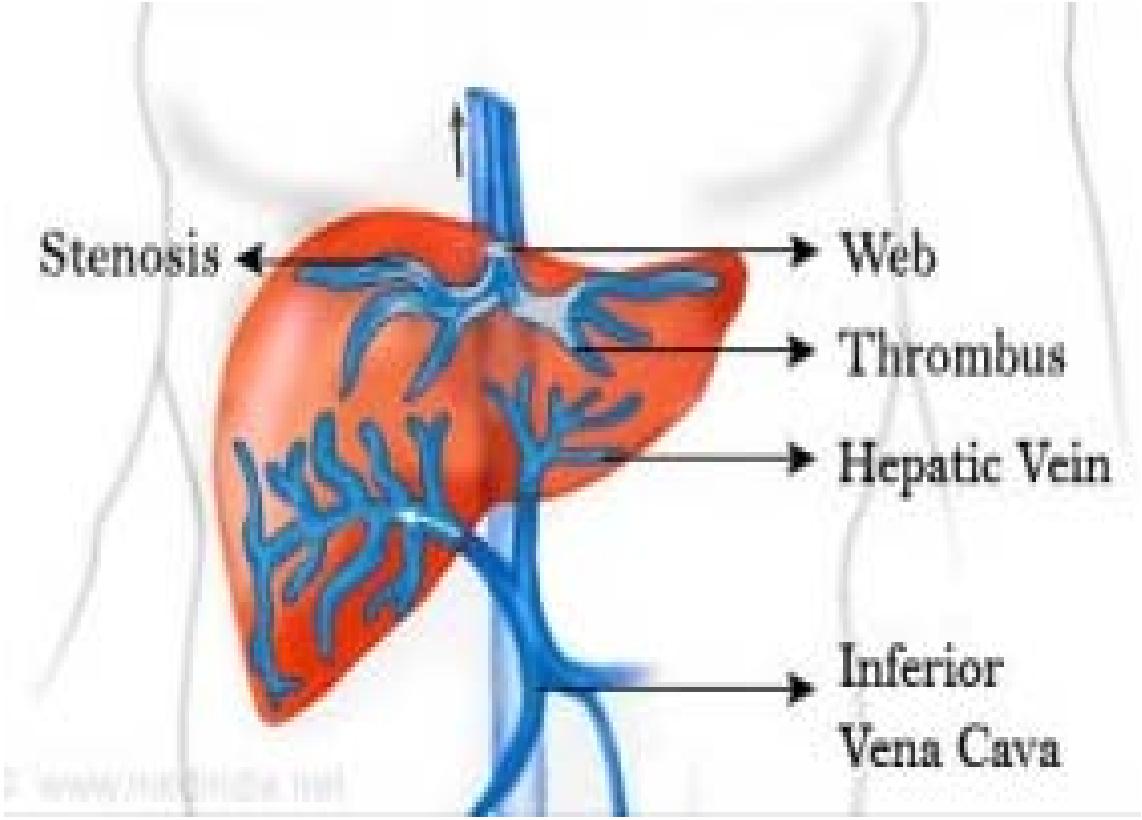
EASL CPG VDL. J Hepatol 2016;64:179–202

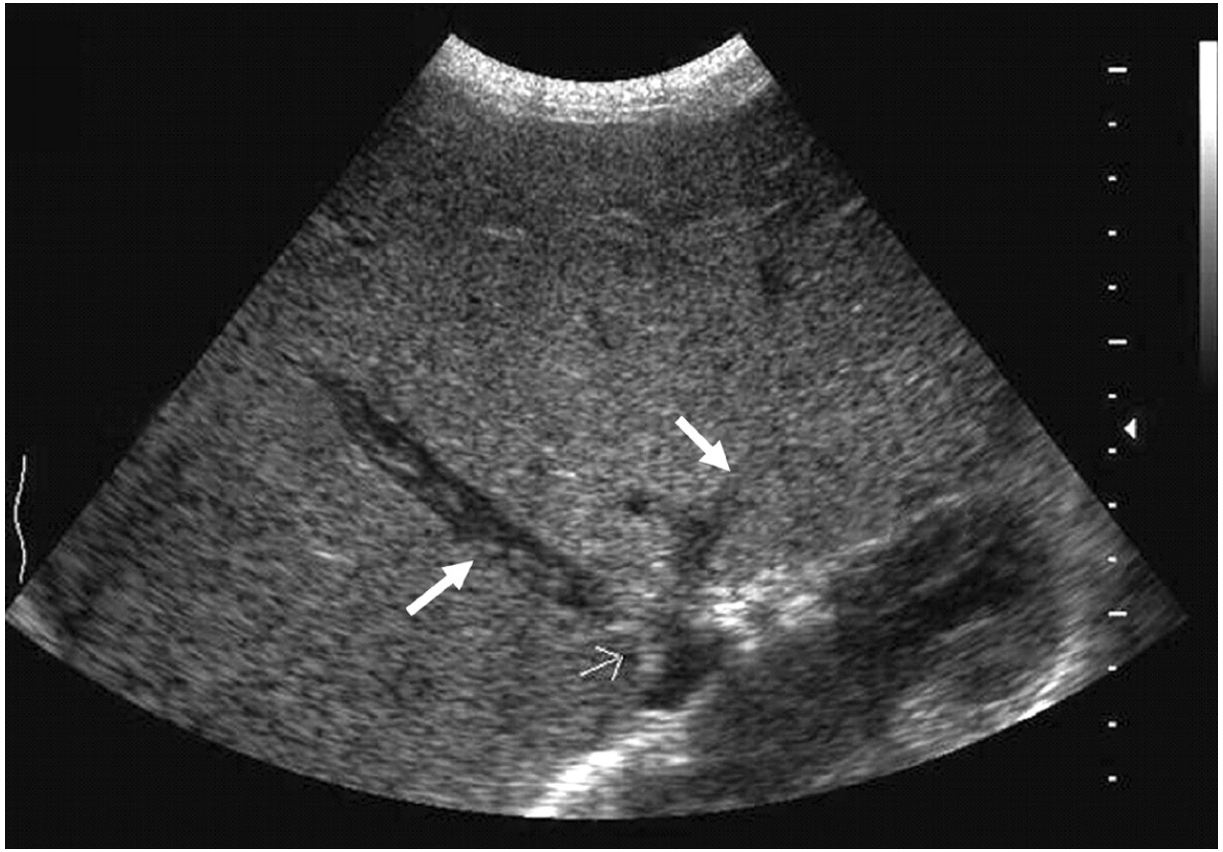
Portal vein thrombosis (PVT)





Sd di Budd Chiari





Budd–Chiari syndrome: Definition and diagnosis

- BCS is defined by the obstruction of hepatic venous outflow
  - **Primary BCS**: caused by thrombosis
    - Western countries: pure hepatic vein thrombosis is the most common
    - Asia: pure IVC or combined IVC/hepatic vein block predominates
  - **Secondary BCS**: other causes, such as malignant invasion

- Pathophysiological consequences of obstruction include:
  - Sinusoidal congestion
  - Liver ischaemia
  - Hepatocellular necrosis

Recommendations		
Consider diagnosis of BCS in any symptomatic or asymptomatic patient with acute or chronic liver disease	A	1
Doppler ultrasound is the first line of investigation for BCS. MRI and CT have to be used for diagnostic confirmation	A	1
Re-evaluate the patient with an expert radiologist in patients with negative imaging studies but a high suspicion of BCS	A	1
Refer patients with BCS to expert centres	A	1

EASL CPG VDL. J Hepatol 2016;

Risk factors in BCS and PVT

Risk factor	BCS frequency (%)	PVT frequency (%)
Thrombophilia		
Inherited	21	35
Acquired	44	19
Myeloproliferative neoplasm	49	21
JAK2V617F positive	29	16
Hormonal factors	38	44
Oral contraceptives	33	44
Pregnancy	6	0
PNH	19	0
Other systemic factors	23	ND
Local factors	0	21

EASL CPG VDL. J Hepatol 2016;64:179–202

Investigations for splanchnic vein thrombosis

- In patients with SVT without an underlying liver disease, diagnosis of the underlying aetiological factors is important

Recommendations		
Investigate patients with BCS and PVT for underlying local and systemic prothrombotic factors. Identification of one risk factor should not deter from looking for additional risk factors	A	1
Work-up consists of diagnosis for inherited and acquired thrombophilia factors, myeloproliferative neoplasms, paroxysmal nocturnal haemoglobinuria and autoimmune disorders	A	1
Investigate patients with both BCS and PVT for local risk factors, including intra-abdominal inflammatory conditions and abdominal malignancies	A	1
Thrombophilia screening should include protein S, protein C and antithrombin levels, FVL mutation, prothrombin *G20210A* gene variant and antiphospholipid antibodies (APAs). In case of APA positivity, this should be repeated after 12 weeks	A	1

EASL CPG VDL. J Hepatol 2016;64:179–202

Investigations for splanchnic vein thrombosis

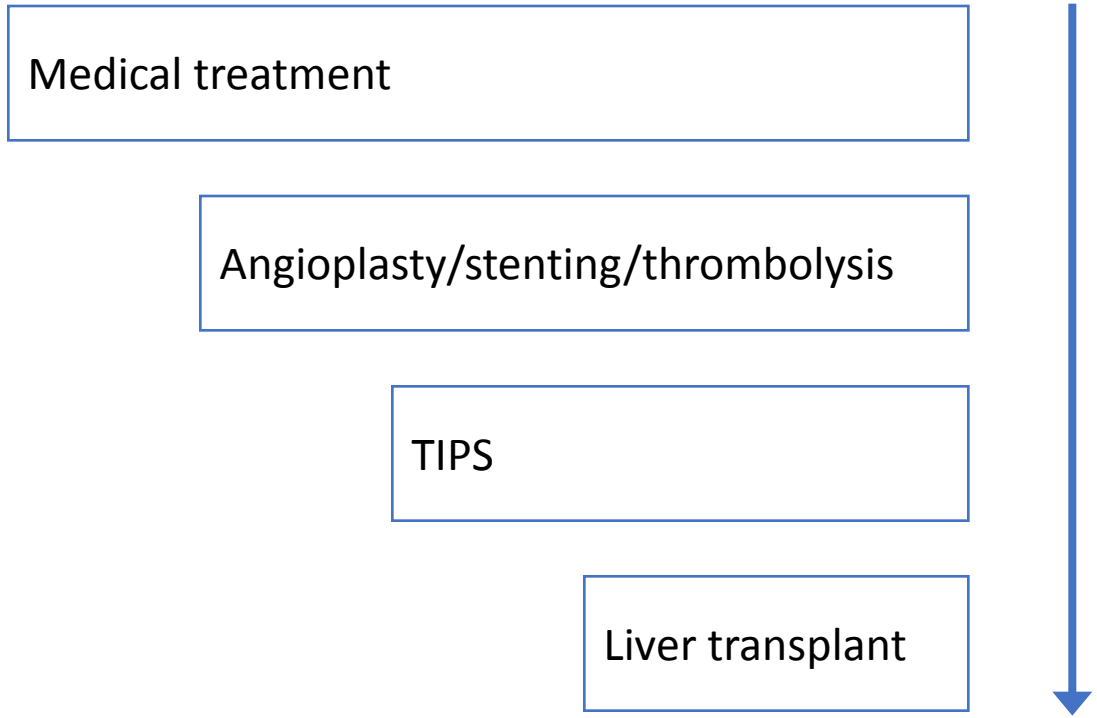
- MPNs are a common underlying cause of abdominal vein thrombosis
  - *JAK2V617F* mutation is of major importance in the diagnostic strategy for MPN

Recommendations	Grade of evidence	Grade of recommendation
Test for MPNs by testing for *JAK2V617F* mutation in SVT patients, and in individuals with normal peripheral blood cell counts	A	1
In JAK2V617F mutation-negative patients, calreticulin mutation screening should be performed and if both are negative, bone marrow histology should be considered. Patients have to be referred to a haematologist	B	2
Treat the underlying condition appropriately	B	1
In case of an underlying MPN, anticoagulant treatment should be given indefinitely for SVT patients	B	1

EASL CPG VDL. J Hepatol 2016;64:179–202

Stepwise therapeutic algorithm for BCS

- Based on retrospective cohorts and prospective series of patients
  - No RCTs



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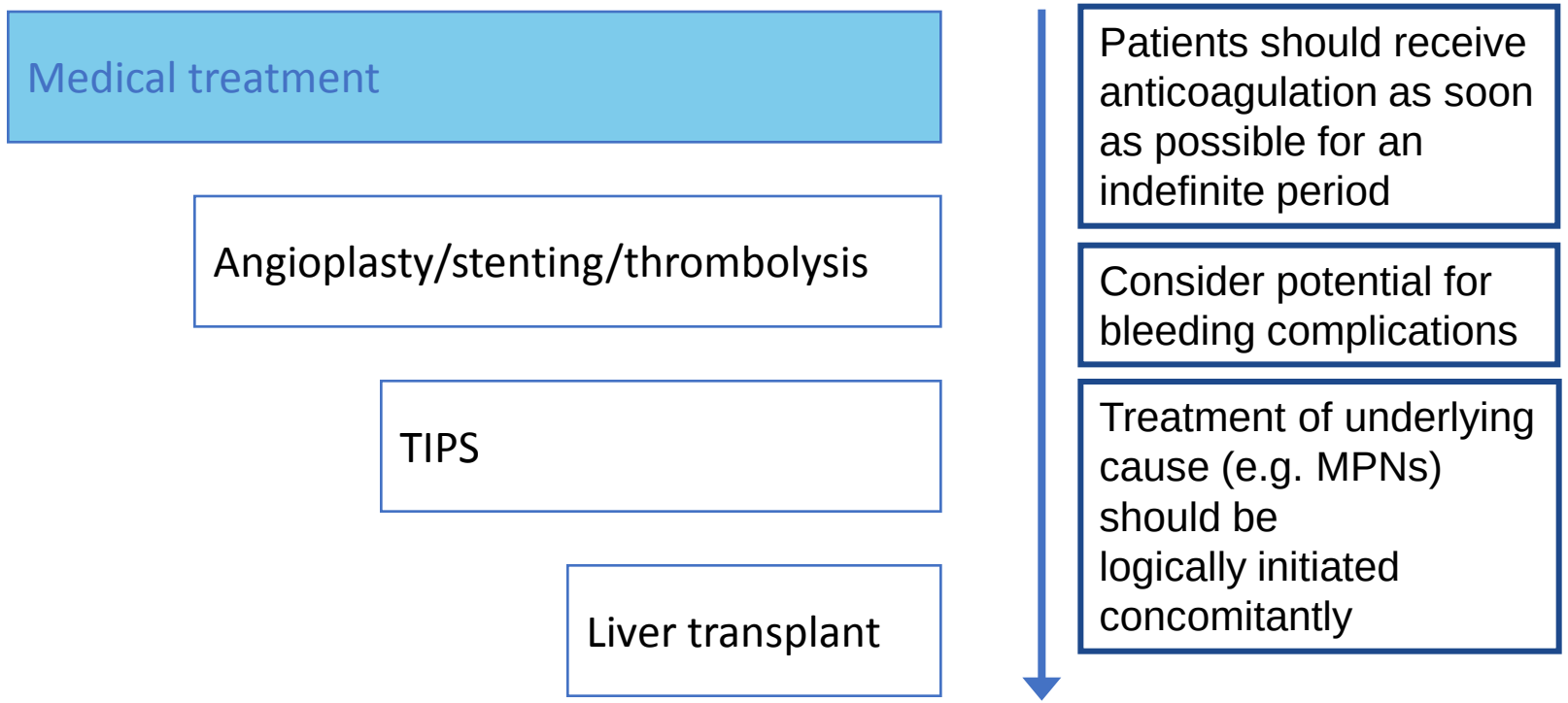

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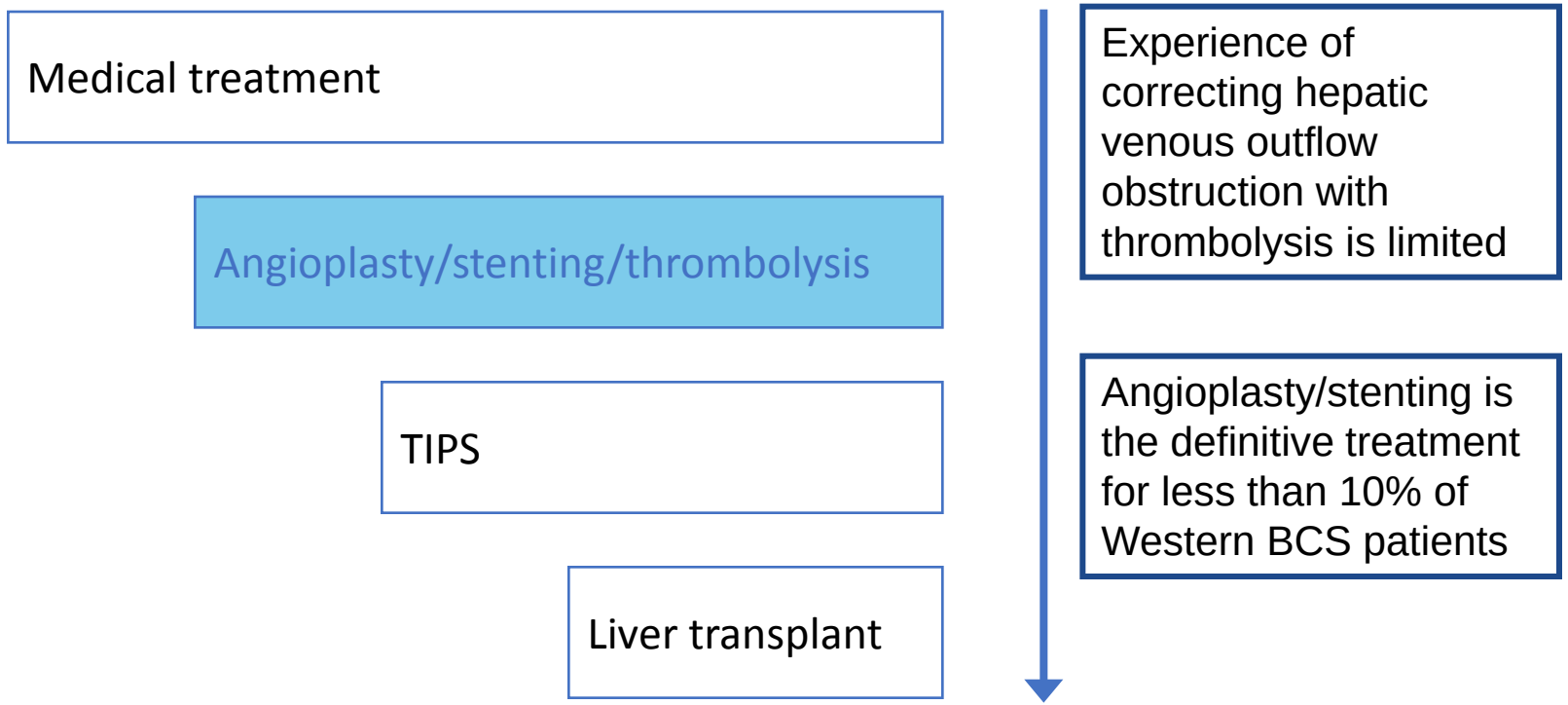
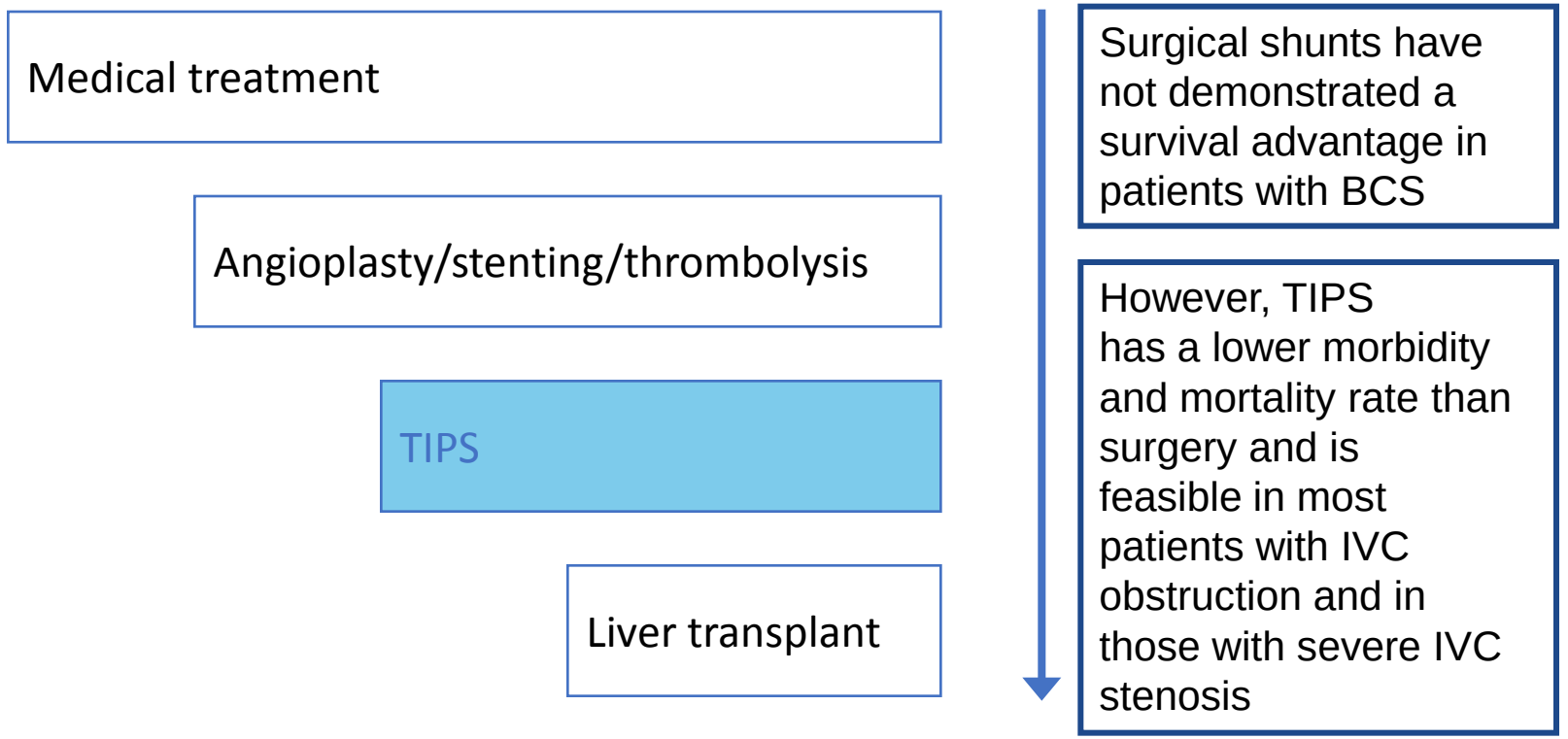


EASL CPG VDL. J Hepatol 2016;64:179–202

EASL CPG VDL. J Hepatol 2016;64:179–202

Stepwise therapeutic algorithm for BCS

- Based on retrospective cohorts and prospective series of patients
  - No RCTs



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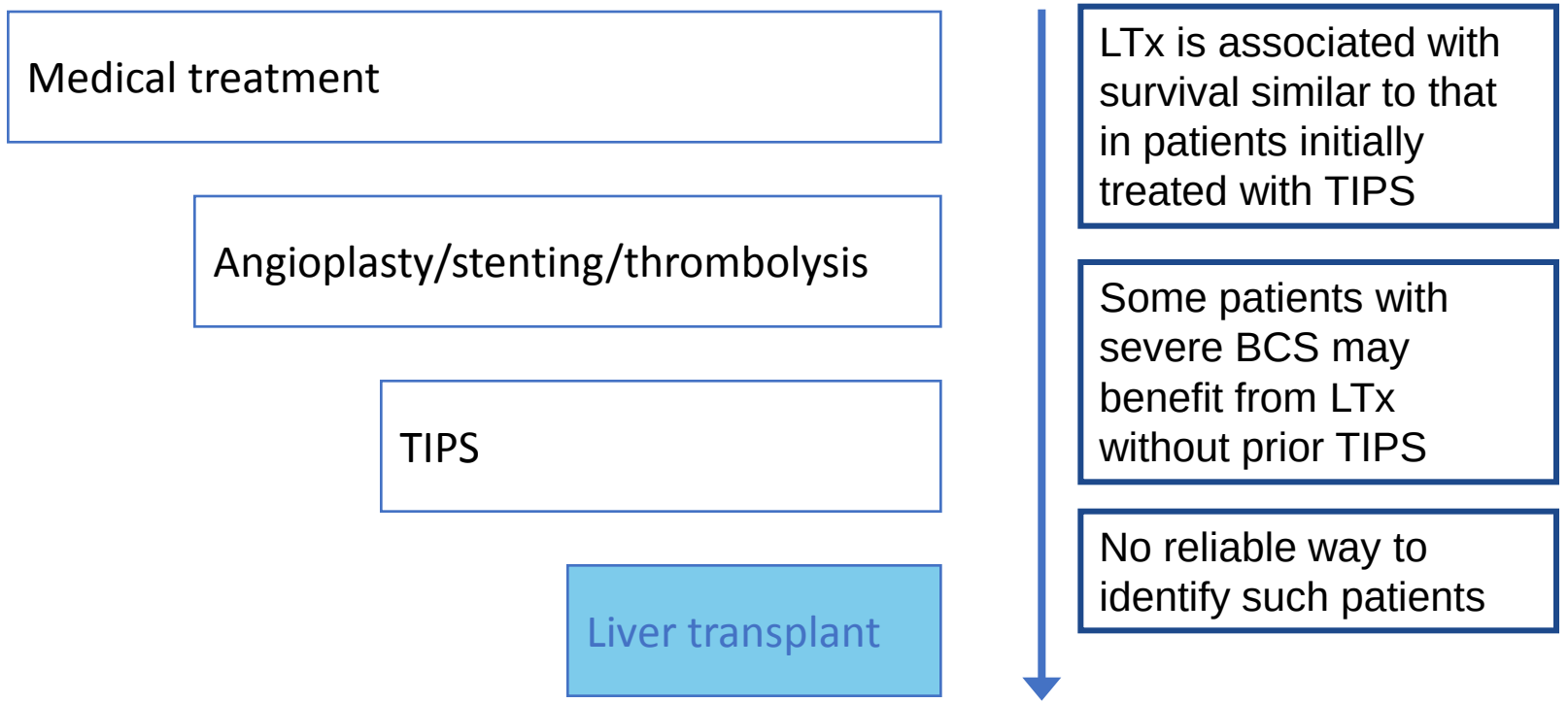
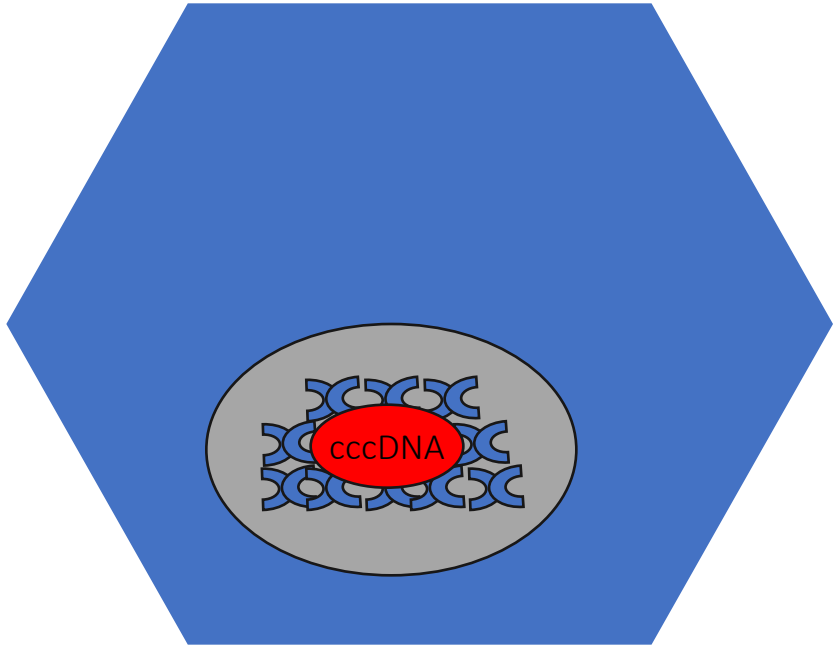


EASL CPG VDL. J Hepatol 2016;64:179–202

EASL CPG VDL. J Hepatol 2016;64:179–202

- ✓Manifestazioni ematologiche in corso di malattie epatiche
- ✓Manifestazioni ematologiche maligne del fegato
- ✓Disordini vascolari del fegato
- ✓Sinusoidal obstructive syndrome (SOS)/Veno Occlusive disease (VOD)
- ✓GVDH
- ✓Riattivazione Virale in corso di Chemioterapia /mAb

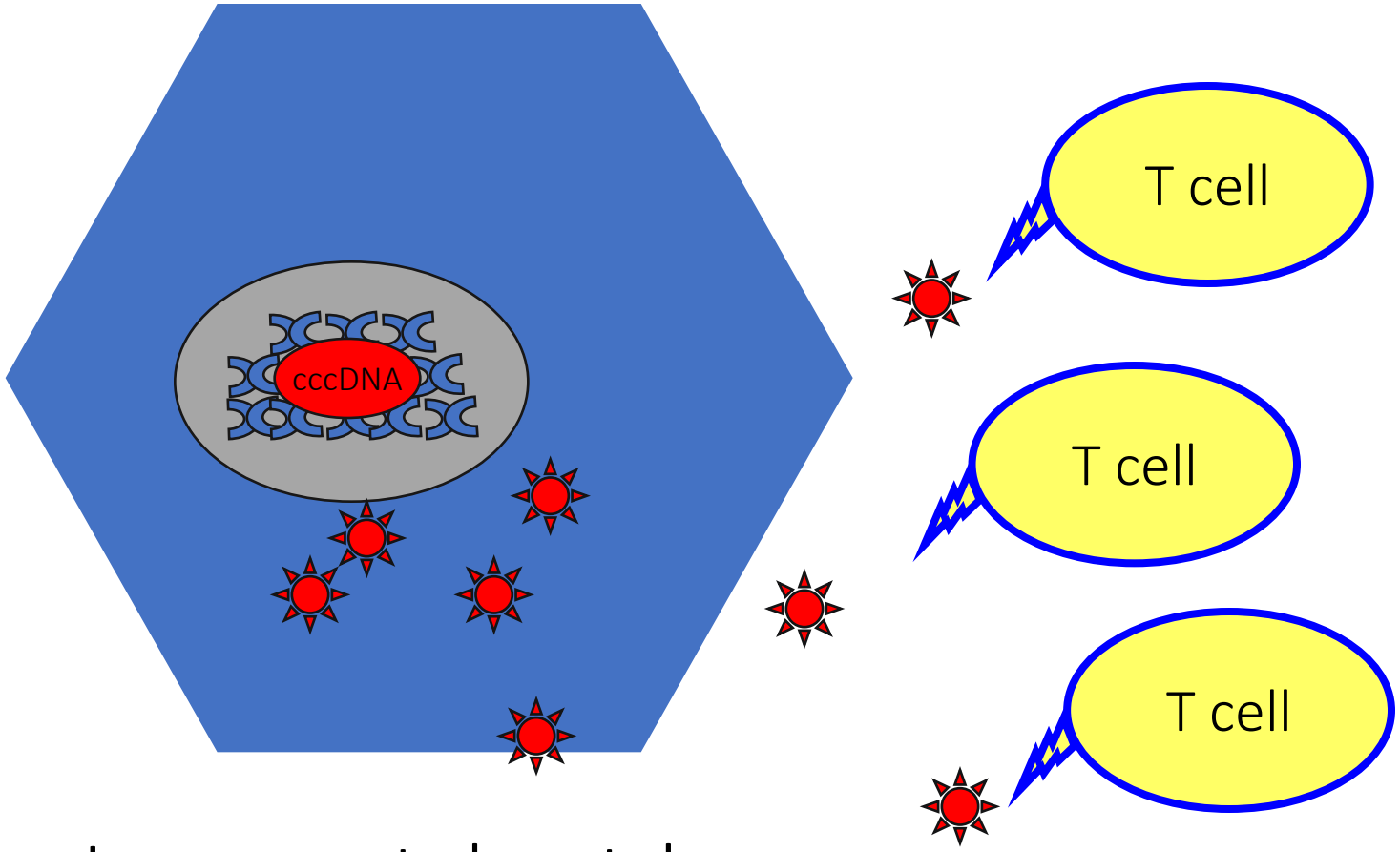
Do You Ever Really Get Rid of HBV?



- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver
- ccDNA—episomal replicative intermediate responsible for persistent infection of hepatocytes

Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758

Do You Ever Really Get Rid of HBV?



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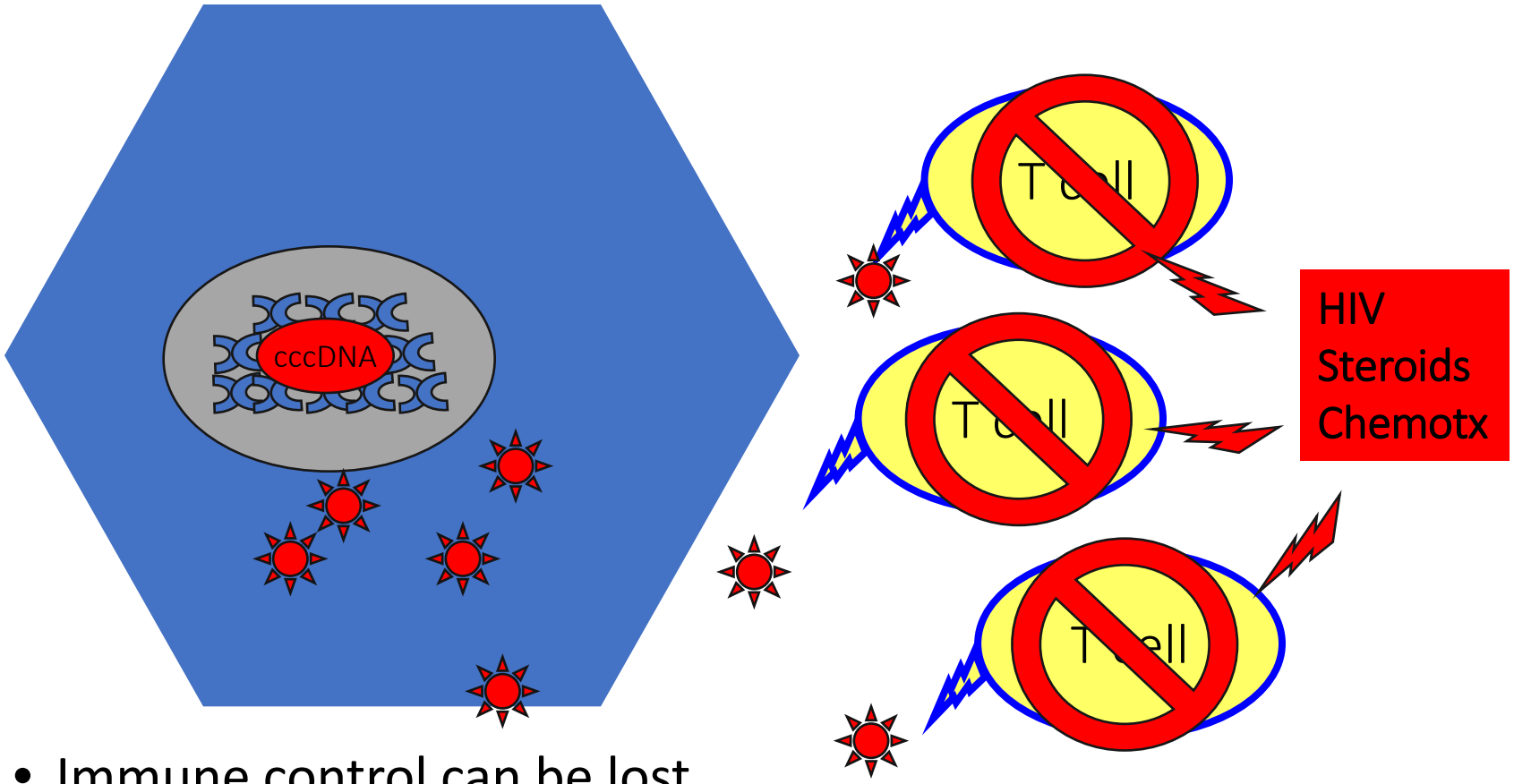
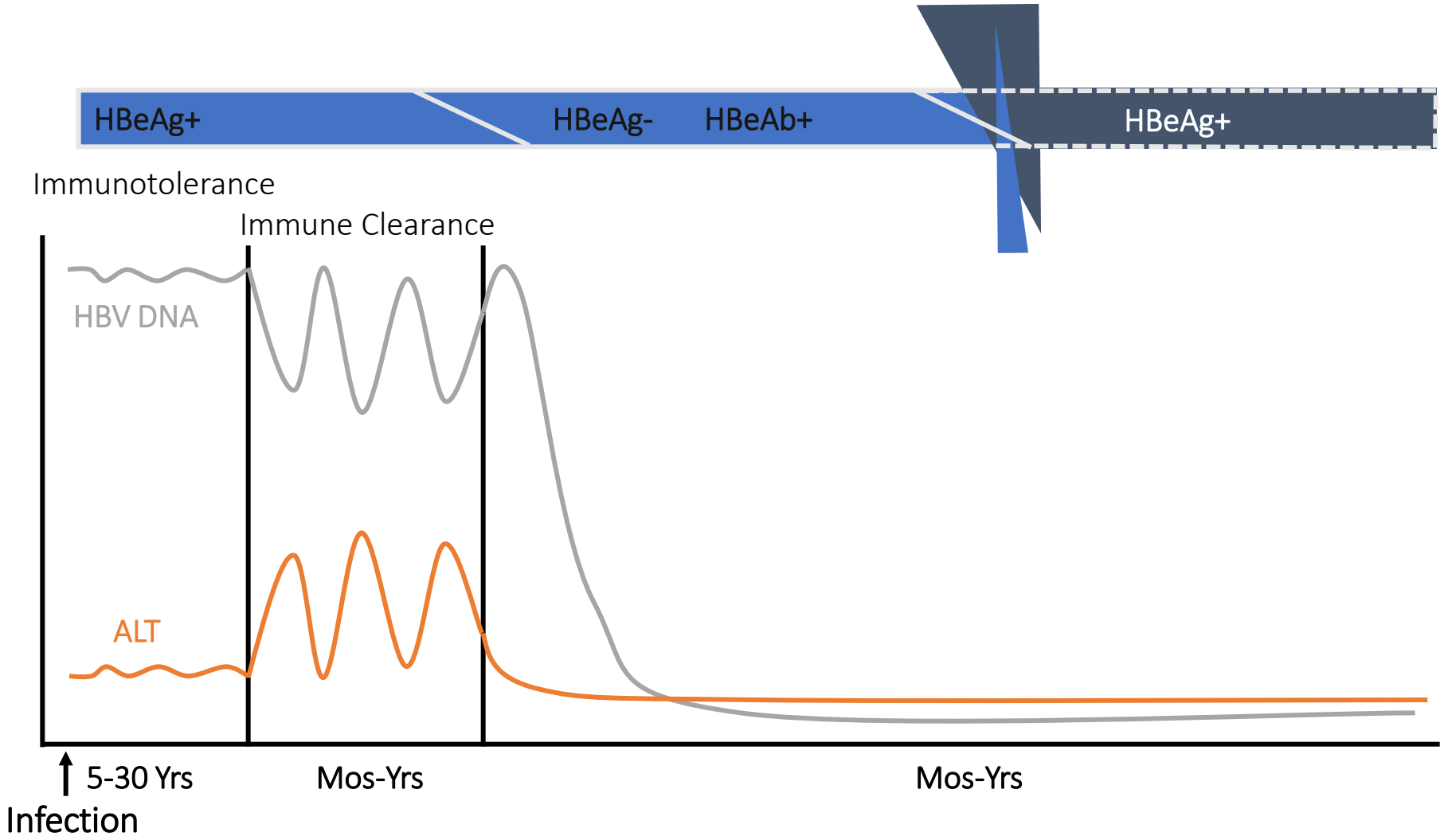
Along Comes Immune Suppression



- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

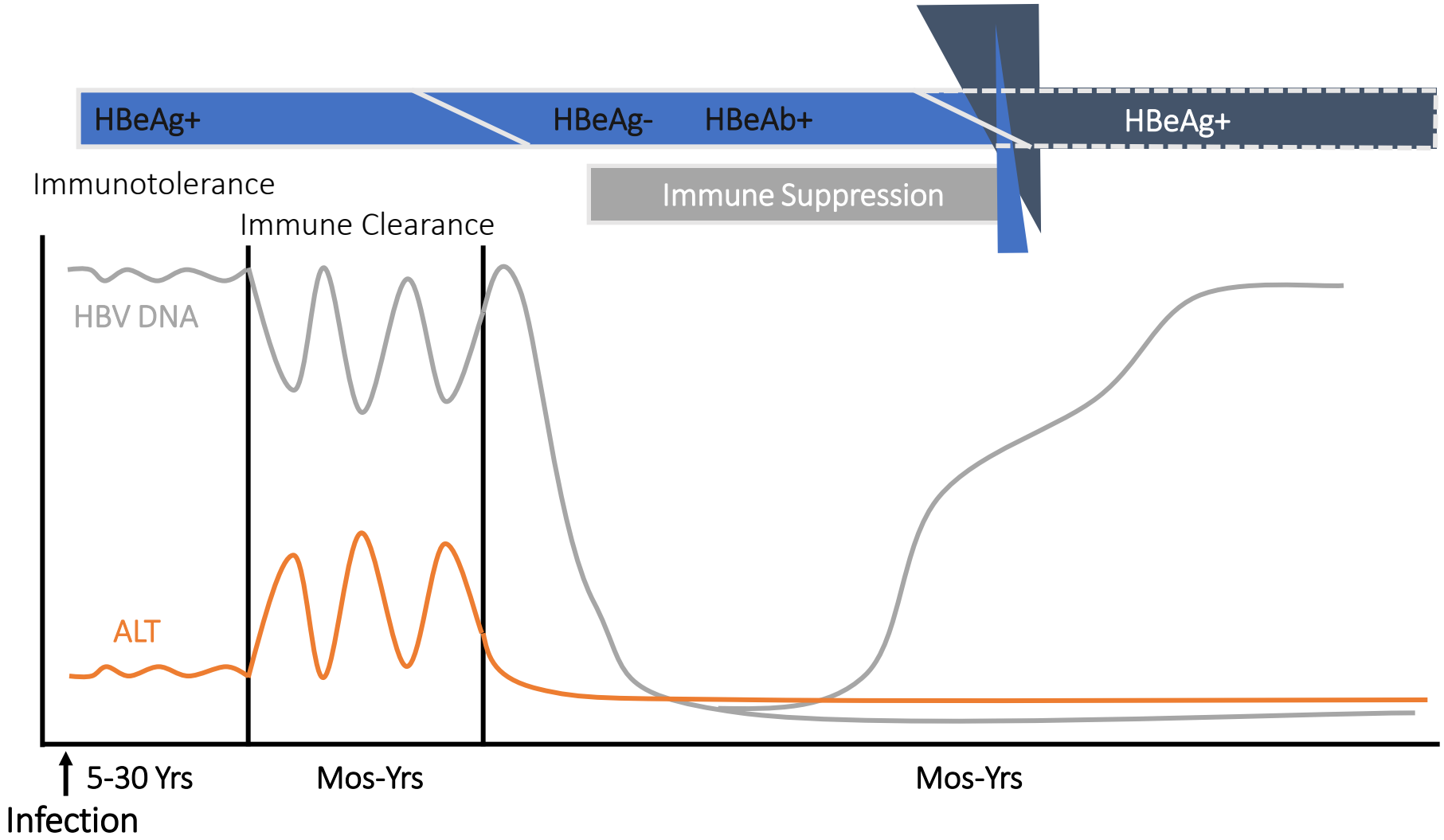
Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

HBV Reactivation



Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

HBV Reactivation



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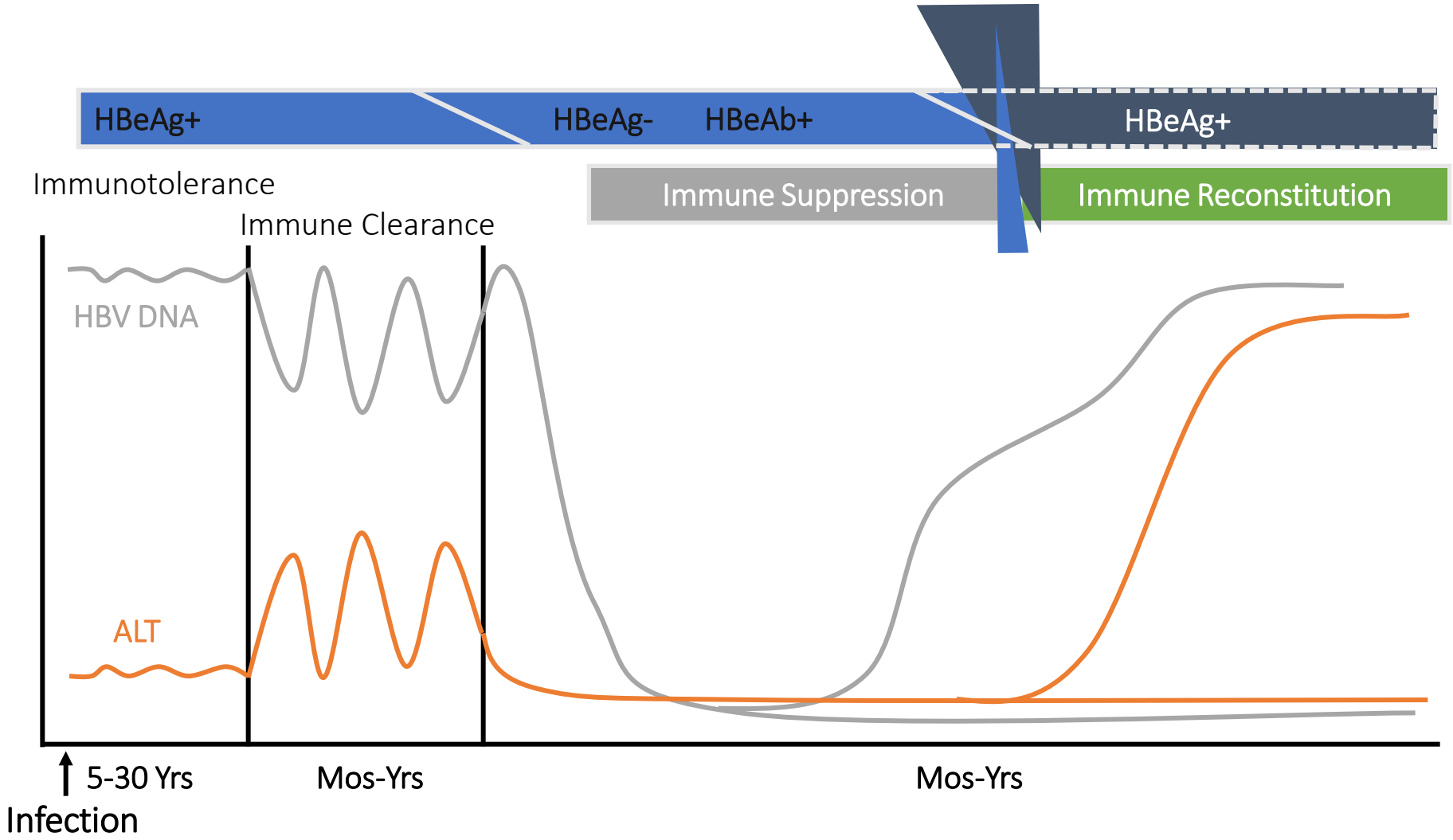
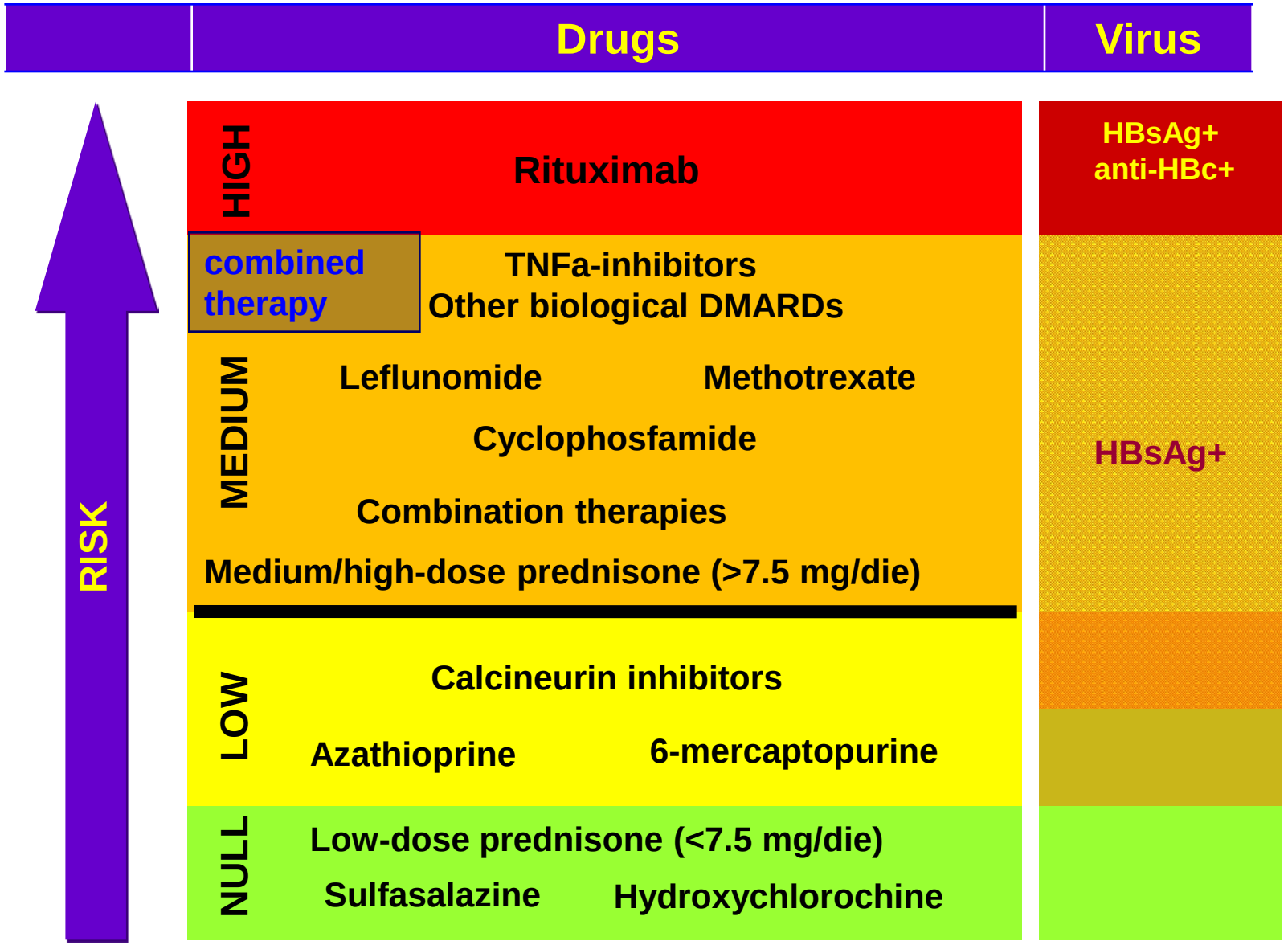
HBV Reactivation



Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

Risk stratification for HBV reactivation



Conclusioni

- **Marker virali per epatite B, Sempre!!!**
- **Contatta l'Epatologo**
- **Trattamento appropriato e monitoraggo sono essenziali per questi pazienti**

Grazie